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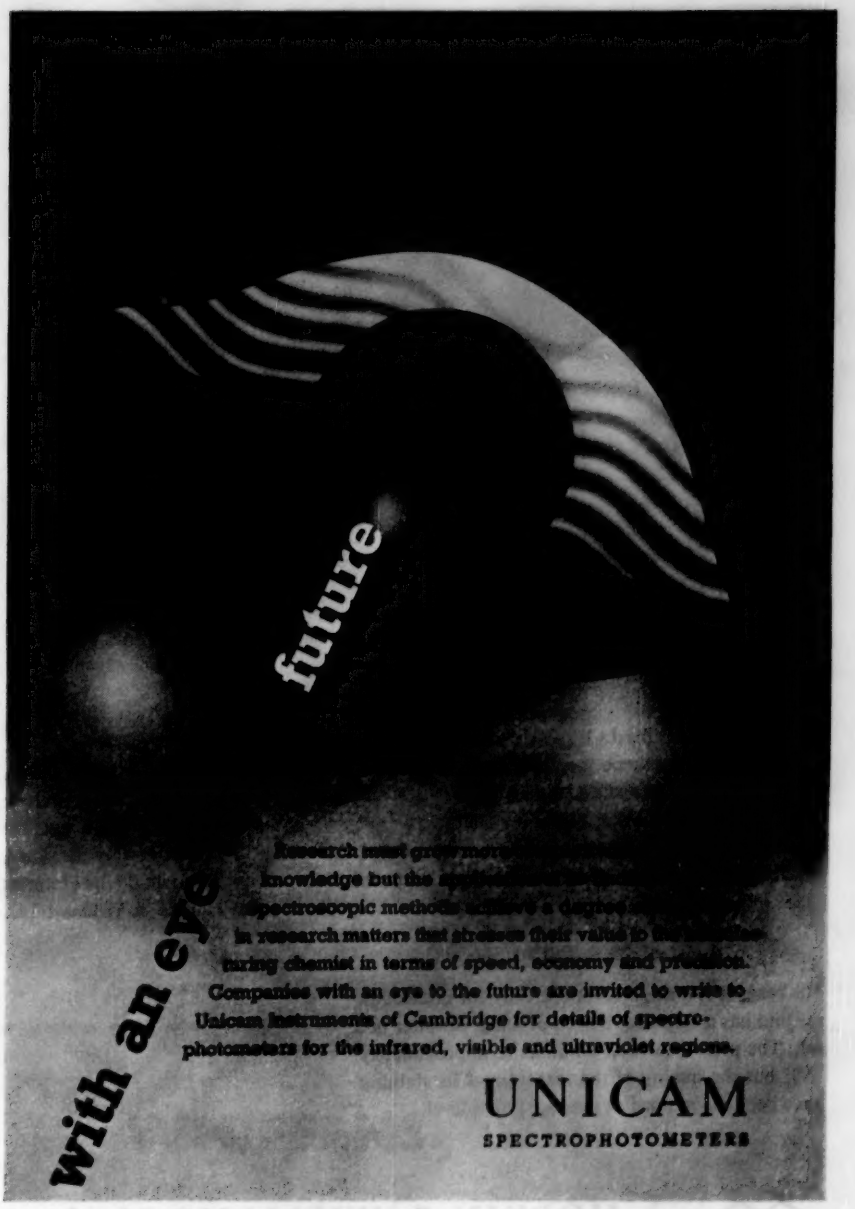
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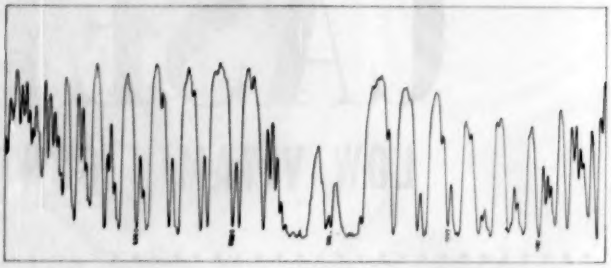

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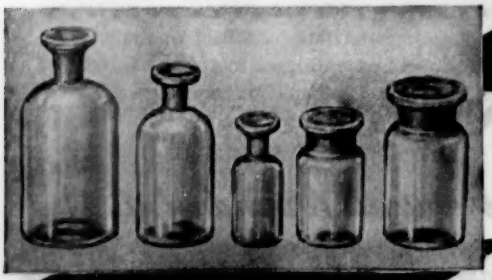

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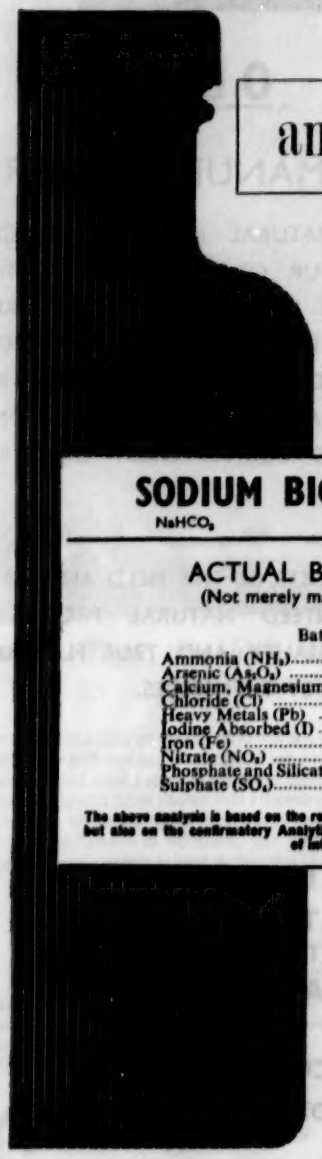

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Heavy Metals (Pb)	0·0002%
Iodine Absorbed (I)	0·0044%
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Proton-acceptor Properties of Azulene.

By Albert Wassermann.

[Reprint Order No. 5715.]

Spectrophotometric and conductometric measurements show that the interaction between tri- and di-chloroacetic acid and azulene in benzene solution involves a proton transfer. The reactions are characterised by equilibrium coefficients, which have been determined within a temperature range of about 40°. The entropy change accompanying the transfer of the proton from the acid to azulene appears to be negative, as in other processes in which the net electrostatic charge increases in passing from the initial to the final state.

Azulene is a proton acceptor (Plattner, Heilbronner, and Weber, *Helv. Chim. Acta*, 1952, **35**, 1036, and references therein) but constants, K, of the equilibrium

$$n \text{ Acid (A)} + \text{Azulene (B)} \rightleftharpoons \text{Azulene–acid adduct} \quad . \quad . \quad . \quad (1)$$

have not yet been measured. The equilibrium constants for the interaction of tri- and di-chloroacetic acid with azulene, in benzene solution, and the molar electrical conductivities of the adducts have now been determined, and some of the results are correlated below with the basic properties of carotene (Wassermann, *J.*, 1954, 4329).

Experimental and Results

Azulene, m. p. 100—102°, was purified by way of the sulphate, chromatographically and by sublimation. The purification of the solvents and chloroacetic acids, and the spectrophotometric and the conductometric techniques, have been described previously (Wassermann, *loc. cit.*). A time-dependence of optical density or of electrical resistance of solutions containing azulene and an acid was eliminated by extrapolation back to the time of mixing.

The light absorption of azulene in benzene solution, without and with the chloroacetic acids, is shown in Fig. 1. The effects are markedly different for the two ranges 320—400 and 400—700 mμ; in the former range the addition of acids brings about an increase of the molar light absorption coefficient, ε, and a shift of $\lambda_{max.}$ to longer wave-lengths, while in the latter range the light absorption is decreased. These changes are due to conversion of azulene into the chloroacetic acid adducts, similar effects with sulphuric acid having been described by Plattner *et al.* (*loc. cit.*) and by Chopard-Dit-Jean and Heilbronner (*Helv. Chim. Acta*, 1952, **35**, 2170). Ethyl trichloroacetate, in contrast to the free acid, does not alter the light absorption of azulene to any significant extent.

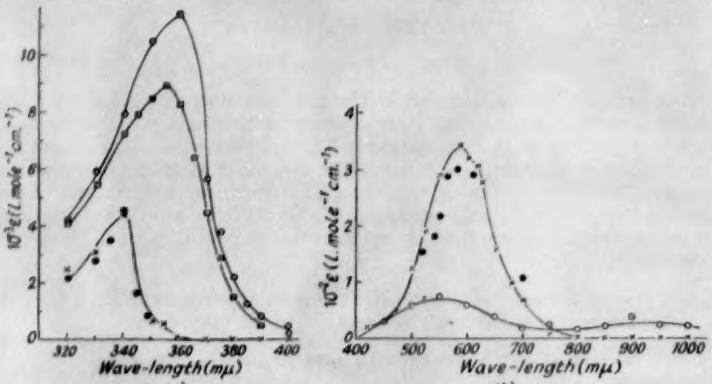
The constant, K, of equilibrium (1) is defined by:

$$K = \frac{[\text{Adduct}]}{[\text{A}][\text{B}]} \cdot \frac{f_{\text{Adduct}}}{f_{\text{A}} f_{\text{B}}} = K' \cdot \frac{f_{\text{Adduct}}}{f_{\text{A}} f_{\text{B}}} = \frac{d_{\text{A}} - d_{\text{B}}}{d_{\infty} - d_{\text{A}}} \cdot \frac{1}{[\text{A}]} \cdot \frac{f_{\text{Adduct}}}{f_{\text{A}} f_{\text{B}}} \quad . \quad . \quad . \quad (2)$$

where the meanings of symbols are as in Wassermann's equation (2) (*loc. cit.*), except that B refers here to the " free " azulene. It is assumed, as previously, that n in equation (1) is unity and that the species in the adduct are held firmly together by electrostatic forces. As the ratio [Adduct]/[B] was varied, K' decreased with decreasing acid concentration. In order to estimate K the empirical extrapolation method described previously was employed.

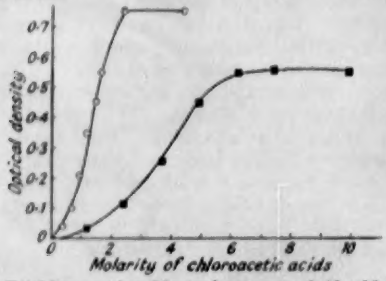
The complete conversion of azulene into the chloroacetic acid adducts, indicated by a limiting value of the optical density, is shown by the typical graphs in Fig. 2. The equilibrium measurements were done with light of 360 or 370 mμ, because at these wave-lengths the light absorption of " free " azulene is not significant, while that of the acid adducts is sufficiently large and in most cases not time-dependent during the first 15—20 min. Attempts were made to carry out equilibrium measurements with light of 600 mμ; however, relatively concentrated solutions have then to be used, and the optical densities are so strongly dependent on time that " back-extrapolation " is not sufficiently accurate. A typical graph showing the dependence of log K' on the acid concentration is in Fig. 3 and the results of the equilibrium measurements are in Tables 1 and 2.

FIG. 1*a*—*b*. *Light absorption of azulene without and with chloroacetic acids in benzene solution at* 20°. [Here and below the molar light absorption coefficient, ε, is as defined by Wasserman (*loc. cit.*).]



× Azulene without acid. ○ Azulene in 2·30M-trichloroacetic acid (azulene completely converted into the adduct). In both sets of experiments the validity of Beer's law was established in the concentration range 1·00—29·2 × 10^{-3} mole of azulene per l.
□ Azulene in 2.30M-dichloroacetic acid (azulene partly converted into the adduct).
● Azulene in 1·51M-ethyl trichloroacetate.

FIG. 2. *Influence of concentration of the two chloroacetic acids on optical density at* 370 mμ, *of benzene solutions of azulene*; 20°; *optical path length* 1·00 *cm.*



○ Trichloroacetic acid; azulene concn. 1·46 × 10^{-4}M.
■ Dichloroacetic acid; azulene concn. 1·24 × 10^{-4}M.

FIG. 3. *Influence of trichloroacetic acid concentration on* log *K'*. *Solvent benzene*; 49·0°.

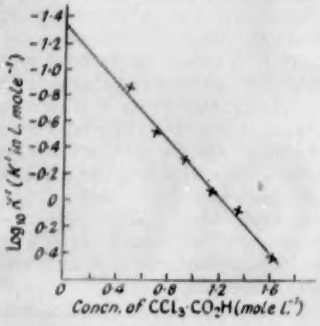
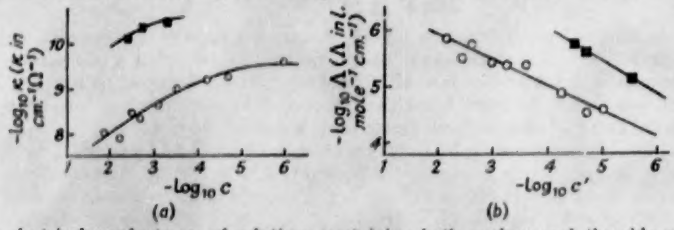


FIG. 4*a*—*b*. *Electrical conductance of azulene in presence of chloroacetic acids*; *solvent benzene*; 25·0°.



κ = Specific electrical conductance of solutions containing both azulene and the chloroacetic acids, extrapolated back to the time of mixing and corrected for specific electrical conductance of the acid without azulene.
c = "Stoicheiometric" azulene concn. (mole l.$^{-1}$).
Λ = Molar electrical conductance of azulene–chloroacetic acid adducts.
c' = Concn. (mole l.$^{-1}$) of azulene–chloroacetic acid adducts.
○ 1·00M-Trichloroacetic acid.
■ 1·00M-Dichloroacetic acid.

Plots of the logarithm of the specific electrical conductance, κ, of solutions containing azulene and acid against the logarithm of the "total" (stoicheiometric) azulene concentration are on the left-hand side of Fig. 4. These values of κ are corrected for the specific electrical conductance

TABLE 1. *Equilibrium between azulene and chloroacetic acids in benzene solution.*

Acid	Concn. of acid (mole l.$^{-1}$)	Concn. of azulene * (10^{-5} mole l.$^{-1}$)	Temp.	No. of runs	K (l. mole^{-1})
Trichloroacetic acid ...	0·460—4·37	29·2	20—21°	9	0·08 ± 0·01
	0·460—4·37	14·6		8	0·08 ± 0·01
	0·460—2·76	4·98		9	0·10 ± 0·01
	0·276—2·30	3·65	18—19	9	0·08 ± 0·01
	0·230—4·14	14·6	8·5	9	0·09 ± 0·01
	0·460—2·30	14·6	35	7	0·06 ± 0·01
	0·460—2·30	14·6	49	7	0·05 ± 0·01
Dichloroacetic acid ...	2·44—6·10	19·0	11	6	0·010 ± 0·002
	1·22—9·76	12·4	17	7	0·010 ± 0·003
	2·44—6·10	19·0	35	5	0·0089 ± 0·002
	2·44—9·76	19·0	49	6	0·010 ± 0·002

* "Stoicheiometric" concns.

TABLE 2. *Influence of added proton acceptors on optical density of a benzene solution of azulene and trichloroacetic acid.*

Temp. 17°; optical path length 1·00 cm.; azulene and trichloroacetic acid concns. respectively $7·00 \times 10^{-5}$ and 2·30 mole l.$^{-1}$.

Added proton acceptor (mole l.$^{-1}$)	Optical density (360 mμ)	Added proton acceptor (mole l.$^{-1}$)	Optical density (360 mμ)
None	0·72	Dioxan (0·467)	0·63
Acetone (4·10)	0·25	(0·720)	0·46
Ethyl alcohol (5·15)	0·08	(0·934)	0·30
		(1·87)	0·05

of 1·00M-tri- and -di-chloroacetic acid without azulene ($4·30 \times 10^{-10}$ and $0·34 \times 10^{-10}$ Ω^{-1} cm.$^{-1}$). The κ value of azulene without acid was so small that the contribution of "free" azulene to the over-all specific electrical conductance could be neglected. By using the results of the equilibrium measurements, the concentration, c', of the azulene–acid adducts was calculated; the molar electrical conductivities, λ, are obtained by dividing the corrected κ values by c'. Plots of log Λ against log c' are on the right-hand side of Fig. 4.

DISCUSSION.

A proton-transfer mechanism of reaction (1) is consistent with the fact that the K values (Table 1) decrease from trichloroacetic acid to the weaker dichloroacetic acid. It explains, moreover, why the optical density of a benzene solution containing azulene and trichloroacetic acid decreases on addition of basic solvents (see Table 2): this must be brought about by a competition of azulene and the added base for the proton from the acid. The basicity of azulene, like that of carotene, is regarded as being due to the π-electrons of the conjugated double bonds. Comparison of Tables 1 of the earlier paper and of this paper show the ratio K (carotene)/K(azulene) exceeds unity for both tri- and di-chloroacetic acid.

This mechanism for reaction (1) is proved by the marked electrical conductivity of the azulene–chloroacetic acid adducts in benzene solution, control experiments having established that the electrical conductivity of solutions containing either the acid or the azulene alone is generally not significant. Comparison of the relevant curves of Fig. 4 of this paper, with the curves in Fig. 7 of the earlier work shows that the molar electrical conductivities of the chloroacetic acid–azulene and the carotene adducts are of the same order of magnitude, the former having the lower electrical conductivity.

The experimental errors of the K values in Table 1 are roughly estimated to be 20—30%. Neither here nor in Table 3 have the standard deviations been computed from the most probable values. As the temperature dependence of K is small, it is obvious that accurate values of the heat and the entropy change of these proton transfer reactions cannot be deduced from the results so far obtained. The values in Table 3 indicate, however, that

TABLE 3. *Heat and entropy changes of proton-transfer processes to unsaturated hydrocarbons.* Solvent, benzene. Temp. range 10—50°.

Hydrocarbon	Proton donor	$-\Delta H$ (kcal.)	ΔS (cal. deg.$^{-1}$)
Carotene *	$CCl_3 \cdot CO_2H$	$2 \cdot 0 \pm 1 \cdot 8$ *	-9 ± 7 *
Azulene	$CCl_3 \cdot CO_2H$	$3 \cdot 0 \pm 2 \cdot 0$	-15 ± 7
	$CCl_2 \cdot CO_2H$	$0 \cdot 0 \pm 2 \cdot 0$	-9 ± 7

* Taken from Wassermann (*loc. cit.*).

the numerical value of $-\Delta H$ is positive, which means that the transfer of the proton is exothermic; and that the corresponding entropy change is negative, as in other processes in which the net electrostatic charge increases on passing from the initial to the final state.

A gift of azulene by Mr. E. Kovatz, Eidgenössische Technische Hochschule, Zurich, is gratefully acknowledged.

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The Constitution of ψ-Santonin. Part IX. Investigations into the Position of the Double Bond.*

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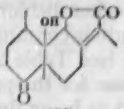
[Reprint Order No. 5731.]

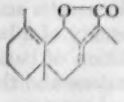
Evidence is presented which indicates that the sesquiterpene, ψ-santonin, has the structure (V).

PREVIOUS investigations in this series have shown that ψ-santonin, $C_{15}H_{20}O_4$, has almost certainly the carbon skeleton (I) (Clemo and Cocker, *J.*, 1946, 30). The sesquiterpene has a lactone ring, a ketone group, a hydroxyl group, and a double bond, and the formula (II) has been advanced as being most in harmony with all the experimental data (Cocker, Cross, and Hayes, *Chem. and Ind.*, 1952, 314). The evidence for the skeleton (I) came from dehydrogenation experiments on compounds derived from ψ-santonin, affording 7-ethyl-1-methylnaphthalene, and from application of the isoprene rule indicating the position of the two carbon atoms eliminated as derived from the angular methyl group

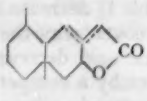
(I)



(II)



(III)



(IV)

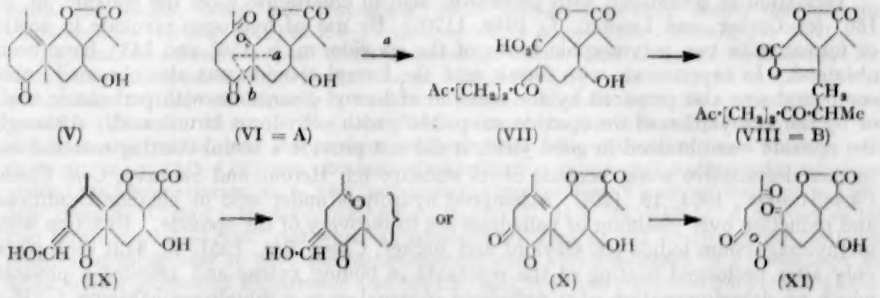
and the carbonyl group of the lactone ring. Further evidence has now been provided by the dehydrogenation of ψ-santonin itself by palladised charcoal in a sealed tube. The reaction affords 7-ethyl-1-methylnaphthalene and a dextrorotatory phenol $C_{15}H_{18}O_3$. Like the desmotropo-ψ-santonins (Clemo and Cocker, *loc. cit.*; Cocker, *J.*, 1946, 36), the phenol on fusion with potassium hydroxide yields 2 : 4-dimethyl-1-naphthol, and so is probably a molecular compound of two of the desmotropo-ψ-santonins. These compounds are produced by the action of acids on ψ-santonin (Clemo and Cocker, *loc. cit.*; Cocker, Cross, and Lipman, *J.*, 1949, 959); in the present case the palladised charcoal is evidently acting as a source of protons (cf. Schmidt, *Chem. Rev.*, 1933, **12**, 363).

It was postulated by Clemo and Cocker (*loc. cit.*) that the lactone ring of ψ-santonin is fused to the perhydronaphthalene nucleus to form the angular (III) rather than linear (IV) polycyclic compound, by analogy with santonin and other terpenes. The lactone

* Part VIII, *J.*, 1951, 929; cf. *Chem. and Ind.*, 1952, 314.

ring undergoes ready hydrogenolysis to give dihydro-ψ-santonin (Clemo and Cocker, *loc. cit.*), and so the double bond must be in the allyl position with respect to the lactone oxygen atom as shown in (III; $\Delta^{1(10)}$, Δ^{7}, or $\Delta^{8(11)}$) and (IV; Δ^{8} or $\Delta^{8(11)}$).

The double bond has now been shown to be in the 1 : 10-position, and ψ-santonin is (V). Ozonolysis of ψ-santonin and reduction of the ozonide with palladised charcoal afford a crystalline solid (A = VI), $C_{15}H_{20}O_6$, m. p. 108°; this results from the cleavage of the double bond, as shown by the absence of the infra-red absorption band of ψ-santonin (1652 cm.$^{-1}$ in Nujol; 1658 cm.$^{-1}$ in $CHCl_3$) due to the double bond. Hydrolysis of (A) with cold aqueous barium hydroxide yields lævulic acid, indicating the presence of the Ac·$[CH_2]_2$·CO group, derived from the decomposition (*b*) of the β-diketone system shown in (VI). The relative positions of the double bond and the keto-group are further demonstrated by ozonolysis of hydroxymethylene-ψ-santonin (IX) in methyl acetate containing methyl alcohol, which affords methyl acetoacetate and acetone: blank experiments show that these are not derived from the solvent, but must have arisen by methanolysis of an oxidation product, probably (XI) (cf. Johnson, Bannister, Bloom, Kemp, Pappo, Rogier, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2275). Again, the base-catalysed reaction of ψ-santonin with butyl nitrite gives a mononitroso-compound which is not the monoxime of (X) since it shows a single absorption maximum at 2830 Å (log ε 4·21) different from that shown by *iso*nitrosocamphor (2410 Å; log ε 3·57) and



dihydro*iso*nitrosoumbellulone (2390 Å; log ε 4·08) (Eastman and Selover, *J. Amer. Chem. Soc.*, 1954, **76**, 4118). It is obvious that the double bond contributes to the absorption of the ψ-santonin derivative.

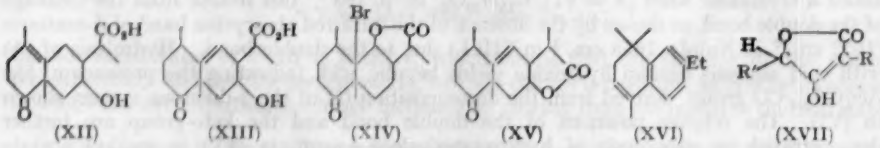
From the evidence given above there can be no doubt that the double bond and the keto-group are in ring A, as shown in (V).

The location of the double bond at 1 : 10 makes it tetrasubstituted and is in harmony with its ultra-violet spectrum (Cocker, Cross, and Hayes, *loc. cit.*) and with the difficulty of its hydrogenation (Clemo and Cocker, *loc. cit.*).

The hydroxyl is thus displaced from $C_{(10)}$, as suggested by Clemo and Cocker (*loc. cit.*), and indeed from ring A, as shown by the production of lævulic acid during the fragmentation of this ring. We have now shown that the hydroxyl group is quantitatively formylated in the cold, and hence is not tertiary, and we place it at position 7 for the following reasons. Under mild alkaline conditions the ozonolysis product (A) gives an isomeric product (B), m. p. 144°. Compound (A) is also converted into (B) and an unidentified compound (C) by boiling water. The properties of (B) are those of a diketo-di-γ-lactone (VIII). In the infra-red region, the product (B) shows peaks at 1704 (Nujol and $CHCl_3$), 1723 (Nujol), and 1732 cm.$^{-1}$ ($CHCl_3$) due to keto-groups, and at 1782 (Nujol) and 1790 cm.$^{-1}$ ($CHCl_3$) due to the butanolide systems. Titration with alkali shows the presence of two lactone systems, one being more stable than the other. We picture the formation of this dilactone as a hydrolysis by route (*a*) of the β-diketone system in (VI), and hence the hydroxyl must be at position 7.

Further evidence for the position of the hydroxyl group of ψ-santonin is derived from the properties of dihydro-ψ-santonin (XIII). Dihydro-ψ-santonin loses water on being melted or heated in acetic anhydride to furnish anhydrodihydro-ψ-santonin (XV); from

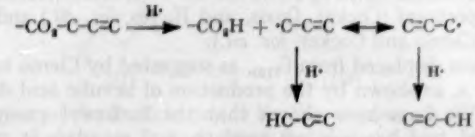
this lactone dihydro-ψ-santonin can be recovered by alkaline hydrolysis (Clemo and Cocker, *loc. cit.*). Anhydrodihydro-ψ-santonin in Nujol absorbs at 1777 (butanolide) and 1698 cm.$^{-1}$ (ketone), but shows no hydroxyl absorption. It must, consequently be the lactone (XV), and its characterisation as a butanolide serves to locate the hydroxyl group in dihydro-ψ-santonin (XIII) and in ψ-santonin (V).



Other methods of degradation have been applied to ψ-santonin, but with less fruitful results. By using permanganate in acetone, the required dihydroxy-derivative was obtained, but in poor yield. This resisted benzoylation and acetylation, as expected if ψ-santonin has the formula (V) since the glycol would be ditertiary. It was oxidised by lead tetra-acetate to the compound (B = VIII), the compound (VI) probably being formed initially and undergoing its ready transformation into (B); the poor yield in this reaction is not surprising in view of the ease with which the product (B) is oxidised further.

Oxidation of ψ-santonin with perbenzoic acid in chloroform gave the epoxide, m. p. 156° (cf. Cocker, and Lipman, *J.*, 1949, 1170). By use of hydrogen peroxide in acetic or formic acids two polymorphic forms of the epoxide, m. p. 156° and 143°, have been obtained. In experiments with formic acid the formyl epoxide was also obtained; this compound was also prepared by the reaction of formyl-ψ-santonin with perbenzoic acid, or by the formylation of the epoxide, m. p. 156°, with anhydrous formic acid. Although the epoxide was obtained in good yield, it did not provide a useful starting material for further degradative work, because of its stability (cf. Herout and Šantavý, *Coll. Czech. Chem. Comm.*, 1954, **19**, 120). Attempted hydrolysis under acid or alkaline conditions and reduction over platinum or palladium led to recovery of the epoxide. Reaction with methylmagnesium iodide (cf. Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413) took place only after prolonged heating of the reactants in boiling xylene and afforded a product which on dehydrogenation over palladised charcoal gave a dihydronaphthalene, $C_{15}H_{20}$. The most probable formula for this compound is (XVI), in which the *gem*-dialkyl group prevents complete aromatisation (cf. Clemo and Dickenson, *J.*, 1937, 255; Cocker *et al.*, *J.*, 1950, 1781).

The ready hydrogenolysis of allyl compounds is possible because of the ease of formation of an intermediate mesomeric radical :



Accordingly dihydro-ψ-santonin might have its double bond in its original position, as in (XII), or shifted to the adjacent position as in (XIII). The latter appears more probable since the bromo-lactone (XIV) formed on treatment of dihydro-ψ-santonin with bromine in sodium carbonate solution (Cocker and Hornsby, *J.*, 1947, 1157) is a butanolide (1763 cm.$^{-1}$; Nujol mull). The compound (XII) cannot readily give a butanolide, whilst (XIII) would be expected to give a butanolide rather than a pentanolide (van Tamelen and Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315). Further dihydro-ψ-santonin shows the light-absorption characteristics of a trisubstituted double bond (cf. Bladon, Henbest, and Woods, *Chem. and Ind.*, 1951, 866; Halsall, *ibid.*, p. 867) as required by (XIII).

Several tetronic acids (XVII) were studied as model compounds at a time when the possibility that the ozonolysis product (A) might be derived from (III; Δ^7) or (IV; Δ^8) was being considered. Tetronic acid and α-methyl-, α-ethyl-, and αγ-dimethyl-tetronic

acid were prepared from acetoacetic ester or its appropriate derivative (cf. Freer, *Amer. Chem. J.*, 1895, **17**, 779; Wolff and Schwabe, *Annalen*, 1896, **292**, 231; Clutterbuck, Raistrick, and Reuter, *Biochem. J.*, 1935, **29**, 316, 1308). For tetronic acid it was preferable to reduce the intermediate bromotetronic acid in methyl alcohol with palladised charcoal, rather than in alkali as recommended by Clutterbuck, Raistrick, and Reuter. In other cases it was found that intensive drying of the bromo-esters before cyclisation improved the yield of the tetronic acids.

The Table summarises some of the properties of the tetronic acids, various β-keto-esters and β-diketones, and the compounds (A), (B), and (C) obtained from ψ-santonin. One of the interesting facts which then emerges is that compounds capable of enolisation to the –C(OH)=CMe–C=O system give a positive iodoform reaction. That iodoform arises *via* the enol is shown by the negative response of the keto-form of 1 : 1-dibenzoylethane. The results also emphasise that the production of iodoform is not an exclusive characteristic of the Me·CO or Me·CH(OH) groups (cf. Booth and Saunders, *Chem. and Ind.*, 1950, 824.).

Experimental

ψ-Santonin shows the following infrared bands in Nujol mull: 3484 and 909 (OH), 1706 (keto), 1753 (1764 in $CHCl_3$) (butanolide), and 1658 cm.$^{-1}$ (C=C). For ultraviolet characteristics, see Cocker, Cross, and Hayes (*loc. cit.*). Dihydro-ψ-santonin shows the following characteristics (without max.) at low wavelength: 2150 Å, ε = 2500; 2200 Å, ε = 2000.

Expoxide of ψ-Santonin.—(*a*) When prepared by Cocker and Lipman's method (*loc. cit.*) with perbenzoic acid the epoxide had m. p. 145—146°, $[\alpha]_D^{11}$ −51·5° (*c*, 2·0 in $CHCl_3$). (*b*) ψ-Santonin (2·64 g.) was kept for a week in a mixture of acetic acid (30 c.c.) and hydrogen peroxide (100-vol.; 12 c.c.). The solvent was removed under reduced pressure, water was added to the residue, and the product was extracted with chloroform from which a solid (2·05 g.; m. p. 131—132°) was obtained Crystallisation from ethyl acetate–light petroleum yielded the above epoxide, m. p. 145°, and from the mother-liquors a second form, m. p. 155—156° (Found: C, 64·1; H, 6·4. Calc. for $C_{15}H_{20}O_5$: C, 64·3; H, 7·1%). A mixture of the two forms melted at 155° and when an alcoholic solution of the lower-melting form was evaporated to dryness it gave the higher-melting form. (*c*) ψ-Santonin (5 g.) was kept for 36 hr. with a mixture of 98% formic acid (25 c.c.) and hydrogen peroxide (200-vol.; 2·11 c.c.) (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786). The mixture was poured into water and neutralised with sodium hydrogen carbonate. The collected solid (3·25 g.; m. p. 145—165°) crystallised from dilute alcohol gave the *formyl-ψ-santonin epoxide* (1 g.) as needles, m. p. 189—190°, $[\alpha]_D^{16}$ −18·9° (*c*, 7·365 in $CHCl_3$) (Found: C, 62·2; H, 6·4. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%). From the mother-liquors ψ-santonin epoxide, m. p. 156° (1·3 g.), was obtained.

Formylation of ψ-Santonin.—ψ-Santonin (0·5 g.) was kept in anhydrous formic acid (2·3 c.c.) for 72 hr., giving the required *formyl* compound (0·5 g.), m. p. 176—177·5° (needles from ethyl acetate), $[\alpha]_D^{16}$ −118·7° (*c*, 1·35 in $CHCl_3$), $\lambda_{max.}$ 2925 Å (log ε 1·68) (Found: C, 65·4; 65·6; H, 6·8, 7·1. $C_{16}H_{20}O_6$ requires C, 65·8; H, 6·8%). When this compound (0·2 g.) was kept with perbenzoic acid (50 mol.) in chloroform it gave the formyl epoxide (0·2 g.; m. p. 188—189°) described above. The latter compound was also obtained (0·15 g.) when ψ-santonin epoxide (0·2 g.; m. p. 155—156°) was kept for 48 hr. with anhydrous formic acid (1 c.c.).

Reaction of ψ-Santonin Epoxide with Methylmagnesium Iodide.—The epoxide (5 g.) in anhydrous xylene (175 c.c.) was added dropwise during 30 min. to a boiling solution of Grignard reagent from magnesium (14·3 g.) in xylene (100 c.c.). The mixture was refluxed for 48 hr. (oil-bath, 170°). The xylene was removed under reduced pressure, and the residue was decomposed with ice and sulphuric acid. The mixture was extracted with ether, and the extract washed with dilute sodium hydrogen carbonate solution, then dried and evaporated, yielding a brown gum (5·5 g.). This was refluxed for 24 hr. in benzene (120 c.c.) with amalgamated zinc (70 g.) and hydrochloric acid (20 c.c.). The reduced compound, a viscous brown oil (5 g.), was passed in a slow stream of hydrogen over 10% palladised charcoal mixed with its own weight of asbestos, at 320—340°, yielding a pale yellow oil (2·2 g.). This was distilled over sodium and the fraction of b. p. 140—160°/14 mm. (0·85 g.) again distilled over sodium, giving a colourless oil (0·25 g.), b. p. 127—130°/2—4 mm., $\lambda_{max.}$ 2320, 2620, (2750), and (2920) [log ε 4·06, 3·23, (3·18), and (3·0) respectively; parentheses denote inflexions]

(Found : C, 89·4; H, 9·6. Calc. for $C_{14}H_{18}$: C, 90·3; H, 9·7. Calc. for $C_{15}H_{20}$: C, 90·0; H, 10·0%). It failed to give an addition compound with picric acid or trinitrobenzene. Heating with selenium for 3 hr. at 335—340° had no effect.

Reduction of ψ-Santonin Epoxide with Lithium Aluminium Hydride.—The epoxide (6·7 g.) was reduced in a Soxhlet apparatus with lithium aluminium hydride (7 g.) in anhydrous ether (300 c.c.) for 6 hr. after all the epoxide had been carried from the thimble (*ca.* 24 hr. in all). The ethereal solution was decomposed with ice and sulphuric acid, the ethereal layer was separated, and the aqueous layer extracted several times with ethyl acetate. The combined extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated, yielding a brown gum (6·0 g.), which when rubbed with light petroleum became solid. After several crystallisations from ethyl acetate the *product* was obtained as rosettes of needles (1 g.), m. p. 179—180°, $[\alpha]_D^{15}$ +51·3° (*c*, 0·77 in EtOH) (Found : C, 62·7; H, 9·4. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·7%). It gave a negative boric acid test for glycols, and was recovered unchanged on attempted oxidation with lead tetra-acetate.

Dihydroxy-ψ-santonin.—A solution of potassium permanganate (4·1 g.) in acetone (300 c.c.) and water (10 c.c.) was added dropwise to a stirred solution of ψ-santonin (4 g.) in acetone (200 c.c.), and the mixture was stirred for 3 hr. It was filtered, and the filtrate concentrated to 10 c.c., saturated with ammonium sulphate, and extracted with ethyl acetate from which a solid (2·65 g.) was obtained. After several crystallisations from ethyl acetate–light petroleum, the *glycol* was obtained as prisms, m. p. 245—246°, $[\alpha]_D^{16}$ +22·4° (*c*, 2·46 in EtOH) (Found : C, 60·6; H, 7·6%; *M*, 315. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4%; *M*, 298). Its 2 : 4-*dinitrophenylhydrazone* (yellow prisms from alcohol) had m. p. 274—276° (Found : C, 53·5; H, 5·6. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·4%).

Oxidation of the Glycol.—This compound (1 g.) in a mixture of anhydrous benzene (50 c.c.), acetic acid (5 c.c.), and methyl alcohol (10 c.c.) was treated with lead tetra-acetate (2 g.), and the mixture was warmed to 50°. It was then set aside for 48 hr. and finally warmed at 50° for 3 hr., after which water was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were evaporated to a yellow gum (0·7 g.). This was triturated with ether, a solid (0·1 g.), m. p. 120—128°, being obtained. Crystallisation from ethyl acetate–light petroleum gave the *compound* (*B*) as needles, m. p. 140—141° (Found : C, 61·0; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·75%).

Ozonolysis of ψ-Santonin to Compound (*A*).—ψ-Santonin (5 g.) in methyl acetate (100 c.c.) was ozonised at −30° to −40° until the ozone was in excess. The solution was then hydrogenated over palladised charcoal (0·2 g.), and after filtration the solvent was removed in a vacuum at room temperature. The gummy product was then kept overnight with water (10 c.c.), needles of *compound* (*A*) (5·1 g.), m. p. 105°, being obtained. Crystallisation from water gave material of m. p. 108—109°, $[\alpha]_D^{17}$ −125°, (*c*, 0·9784 in EtOH), $\lambda_{max.}$ 2830 Å (ε 70) in EtOH (Found : C, 61·0; H, 6·9. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·75%). It gave a positive iodoform test, strongly reduced ammoniacal silver nitrate, Tollens's reagent, Fehling's solution, and alkaline methylene-blue, and consumed one mol. of periodate in alkaline solution. However, the Schiff and the Angeli–Rimini test for aldehydes were negative. When tested on paper with a spray containing sodium nitroprusside and piperazine, it gave a pink colour instead of the blue colour characteristic of the pyruvyl group (Acklin, *Biochem. Z.*, 1925, **164**, 312; Edward and Waldron, *J.*, 1952, 3631). With a spray of alkaline 3 : 5-dinitrobenzoic acid it gave a yellow, while pyruvic acid gave a purple, colour.

Hydrolysis of (*A*) *to Lævulic Acid.*—(*a*) The compound (A) (0·7 g.) was dissolved in 2·8% aqueous barium hydroxide (20 c.c.) at room temperature. After 3 hr. the barium was exactly precipitated with sulphuric acid, and the solution freed from barium sulphate was submitted to chromatography on Whatman No. 1 filter paper. Zones having R_F values similar to that of lævulic acid were obtained with the solvent systems butanol–pyridine–ethanol–water (66 : 12 : 4 : 18 by vol.) (R_F 0·64—0·68) or butanol saturated with aqueous 0·75N-ethylamine (R_F 0·74—0·80). The sprays used were Tollens's reagent, 2 : 4-dinitrophenylhydrazine, and aqueous alkaline sodium nitroprusside.

(*b*) The compound (A) (10 g.) was treated as above with 3·9% barium hydroxide solution (200 c.c.). One-fifth of the barium-free solution was distilled at 30 mm., first on a water-bath and then from an oil-bath, the strongly acidic fraction (0·6 g.; 60% of lævulic acid, by titration; about 45% of theory), b. p. 136—138°, being collected. Its 2 : 4-dinitrophenylhydrazone had m. p. 205° (from alcohol) undepressed by the corresponding derivative of lævulic acid (Braude and Jones, *J.*, 1945, 498), and its semicarbazone had m. p. and mixed m. p. 188° (decomp.) (Perkin and Simonsen, *J.*, 1907, **91**, 827).

Isomerisation of Compound (A) to (B).—When a solution of (A) in chloroform was slowly passed through a column of alumina and the issuing solution evaporated to dryness it gave the product (B), m. p. 126—140°, which after crystallisation from water was obtained as needles, m. p. 144°, $[\alpha]_D^{15}$ −2° (*c*, 3·355 in $CHCl_3$), $\lambda_{max.}$ 2780 Å (ε = 37) in EtOH (Found: C, 60·85; H, 6·65. Calc for $C_{15}H_{20}O_4$: C, 60·8; H, 6·75%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 205—207° (decomp.) (Found: C, 52·65; H, 5·2. $C_{21}H_{24}O_9N_4$ requires C, 52·9; H, 5·0%). The same 2 : 4-dinitrophenylhydrazone was afforded by (A), which apparently isomerised to (B) under the acidic conditions of the reaction. The compound (B) gave a pink colour with nitroprusside–piperazine and a yellow colour with alkaline 3 : 5-dinitrobenzoic acid. Oxidation of (B) (0·25 g.) with sodium hypoiodite (10 g.) gave iodoform (0·12 g., 0·3 mol.) and oxalic acid (0·036 g., 0·5 mol.).

Conversion of (A) into (B) and (C).—When compound (A) (1 g.) in water (10 c.c.) was boiled for 6 hr. and the aqueous solution extracted with chloroform it gave compound (B) (0·25 g.) and from the aqueous solution by evaporation a *product* (*C*) which on crystallisation from water was obtained as rhombs, m. p. 186°, $[\alpha]_D^{17}$ −217·4° (*c*, 1·85 in acetone), $\lambda_{max.}$ 2870 Å (ε = 60) in EtOH (Found: C, 57·3; H, 7·35. $C_{15}H_{20}O_6,H_2O$ requires C, 57·3; H, 7·0%). The infrared absorption in a Nujol mull shows peaks at 1712 (ketone), 1754 (lactone carbonyl), and 3400, 3200, and 900 cm.$^{-1}$ (hydroxyl). The compound gave a yellow colour with nitroprusside–piperazine and a lilac colour with alkaline 3 : 5-dinitrobenzoic acid solution.

Chromatographic Examination of Compounds (A), (B), and (C).—These compounds were boiled with water and with dilute acid and alkali, and the solutions examined for pyruvic acid by chromatography on Whatman No. 1 filter paper with developing solvents: (1) ethanol–pyridine–water (80 : 12 : 8 by vol.), and (2) ethanol–water (1 : 1 by vol.) with a trace of formic acid. Zones were shown by spraying with Tollens's reagent and acidic 2 : 4-dinitrophenylhydrazine solution; R_F values were:

	Compound A	Compound B	Compound C	Pyruvic acid
Solvent 1	0·81	0·80—0·81	0·77—0·81	0·40—0·41
Solvent 2	0·82—0·85	0·82—0·85	0·63—0·64	0·73—0·76

The absence of pyruvic acid from these compounds and from the crude ozonolysis product was clearly shown by using solvent (1). Separations with solvent (2) were uncertain and erratic and the zone attributed to pyruvic acid in a preliminary communication (Cocker, Cross, and Hayes, *loc. cit.*) was probably due to compound (B) or (C). Compound (A) probably isomerised to (B) in the solvent systems employed.

Hydroxyimino-ψ-santonin.—ψ-Santonin (2·4 g.) was added to a solution of sodium (0·5 g.) in absolute alcohol (40 c.c.) and the solution was cooled to −5°. Butyl nitrite (0·9 g.) in alcohol (5 c.c.) was added and the mixture was kept at −5° for 2 hr. and then overnight at 0°. Solvent was removed in a vacuum at 40°, and the residue was dissolved in water and acidified. The gummy product (1·1 g.) was extracted with sodium hydrogen carbonate solution, and the extract was acidified, giving a semisolid material which when rubbed with ether gave a product, m. p. 234—238°. Crystallisation from dilute methyl alcohol gave the required *hydroxyimino-compound*, m. p. 238° (decomp.), as pale yellow needles giving a red ferric reaction, $\lambda_{max.}$ 2830 Å (log ε 4·21) in EtOH (Found: C, 61·6; H, 6·8; N, 4·85. $C_{15}H_{19}O_6N$ requires C, 61·4; H, 6·5; N, 4·8%).

2 : 6-*Di*(*hydroxyimino*)cyclo*hexanone*, prepared by a similar method (but cf. Pezold and Shriner, *J. Amer. Chem. Soc.*, 1932, **54**, 4710), had m. p. 233° (cf. Borsche, *Chem. Zent.*, 1909, 1549, who gives an indefinite m. p. over 200°), $\lambda_{max.}$ 2710 Å (log ε 4·153) (Found: C, 46·2; H, 5·2; N, 18·5. $C_6H_8O_3N_2$ requires C, 46·2; H, 5·1; N, 18·0%).

Hydroxymethylene-ψ-santonin.—Finely powdered ψ-santonin (2 g.), suspended in ethyl formate (7 c.c.), was added to dry sodium methoxide (from sodium, 0·4 g.), and the mixture was chilled to 0°, shaken until solution was obtained, and kept overnight at room temperature. Solvent was removed in a vacuum at room temperature and the solid residue was dissolved in the minimum of water, filtered, and added to a stirred mixture of ice and hydrochloric acid. The resultant oil quickly solidified on stirring, and the solid (2·1 g.), m. p. 185°, was collected and crystallised from ethyl acetate, yielding the *hydroxymethylene-compound* as pale yellow needles (1·5 g.), m. p. 195°. It gave a deep violet ferric reaction (Found: C, 66·1; H, 6·8. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·8%). Its *acetate*, made in alkali, consisted of colourless plates, m. p. 164—165° (Found: C, 64·6; H, 6·71. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%). These compounds were hydrolysed by alkali to ψ-santonin.

Ozonolysis of Hydroxymethylene-compound.—This compound (4·9 g.) in methyl acetate

(15 c.c.; dried over Na_2SO_4, and distilled, but containing a little methyl alcohol) was ozonised at −40° to −50° until the solution became deep blue. The product was hydrogenated over palladised charcoal and, after filtration, the solvent was removed in a vacuum at room temperature, formaldehyde being trapped in 2 : 4-dinitrophenylhydrazine hydrochloride. The oily residue was then distilled in steam into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. From this solution methyl acetoacetate 2 : 4-dinitrophenylhydrazone (0·2 g.), m. p. 105°, was obtained which after crystallisation from methyl alcohol had m. p. and mixed m. p. 119° (cf. Johnson, *J. Amer. Chem. Soc.*, **1951**, **73**, 5888), $\lambda_{max.}$ 2225, (2500), and 3570 Å [log ε = 4·36, (4·07), 4·21 respectively] (Braude and Jones, *J.*, **1945**, 498, give 3580 Å, log ε 4·31, for the acetoacetic acid derivative (Found : C, 44·4; H, 4·0; N, 19·6. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·1; N, 18·9%). The aqueous mother-liquors, which gave a red-yellow ferric reaction, were evaporated to dryness and refluxed for 2 hr. with chloroform (100 c.c.), formic acid (90%; 100 c.c.), and hydrogen peroxide (100-vol.; 15 c.c.) (cf. Prelog and Kocór, *Helv. Chim. Acta*, **1947**, **31**, 237) but gave no further volatile carbonyl compound. An intractable gum was left when the solvents were removed.

In a second experiment in which one mol. of methyl alcohol was added to the methyl acetate, and the 2 : 4-dinitrophenylhydrazones of the products separated by chromatography on alumina with benzene and benzene–ethanol as eluants, the derivatives of methyl acetoacetate, formaldehyde, and acetone (m. p. 118°, 167°, and 128° respectively) were obtained, the last in greatest amount.

Dehydrogenation of ψ-Santonin (cf. Clemo and Cocker, *loc. cit.*).—ψ-Santonin (2·5 g.) was heated at 250—270° for 72 hr. with palladised charcoal. The product was then powdered and extracted with chloroform, which was washed first with sodium carbonate and then with sodium hydroxide solution. Three fractions were thus obtained. The carboxylic acid fraction proved intractable, but from the sodium hydroxide solution a phenolic fraction was obtained and from the chloroform a neutral fraction.

The phenol was obtained as a dark solid, which on sublimation in a vacuum gave a yellow solid, m. p. 158—168°. Crystallised several times from a mixture of benzene and light petroleum and then dilute alcohol the *phenol* (0·5 g.) was obtained as needles, m. p. 210—212°, $[\alpha]_D^{16}$ +138° (*c*, 0·51 in EtOH) (Found : C, 72·7; H, 6·9. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Fused with potash it gave 2 : 4-dimethyl-1-naphthol, m. p. 78—79° (cf. Clemo and Cocker, *loc. cit.*; Cornforth, Cornforth, and Robinson, *J.*, **1943**, 168), characterised as its picrate, m. p. 143°.

The combined neutral fractions (3·3 g.) from several experiments, when distilled from sodium, gave an oil (0·2 g.), b. p. 80—100°/10 mm., from which the picrate of 7-ethyl-1-methylnaphthalene, m. p. 90°, was obtained.

ψ-Santonin hydrazone was obtained as colourless plates (from dilute alcohol), m. p. 249—250° (Found : C, 63·9; H, 7·9. $C_{15}H_{22}O_3N_2$ requires C, 64·7; H, 7·9%). Repeated heating with dilute alcohol leads to decomposition.

Deoxy-ψ-santonin.—(*a*) A mixture of ψ-santonin (2·4 g.), potassium hydroxide (1·75 g.), ethylene glycol (15 c.c.), and hydrazine hydrate (1·3 c.c.; 100%) was refluxed for 1·5 hr. Heating was continued whilst the temperature rose to 187°, at which it was maintained for 4 hr. The *product* (0·2 g.) crystallised from dilute alcohol as needles, m. p. 250°, $[\alpha]_D^{18}$ +30° (*c*, 0·606 in $CHCl_3$) (Found : C, 72·1; H, 9·2%; *M*, 264. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%; *M*, 250). (*b*) ψ-Santonin (2 g.) was refluxed for 43 hr. with hydrazine hydrate (20·5 c.c.; 100%) and a solution of sodium (4 g.) in ethylene glycol (65 c.c.). The *product* (0·2 g.) crystallised from dilute alcohol as needles, m. p. 204—205° (Found : C, 72·8; H, 8·8%), which gave no carbonyl reactions. The two forms are polymorphic.

Reduction of Anhydrodihydro-ψ-santonin.—This compound (0·1 g.) was reduced in glacial acetic acid (10 c.c.) over palladised charcoal at slightly above 1 atm. The *lactone* (0·1 g.) crystallised from dilute alcohol in leaflets, m. p. 157—158°, depressed to 140° by anhydrodihydro-ψ-santonin (Found : C, 72·0; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

Tetronic Acids.—Tetronic acid. Ethyl acetoacetate was brominated and cyclised to α-bromotetronic acid by the methods of Wolff and Schwabe and of Clutterbuck, Raistrick, and Reuter (*loc. cit.*). The crude bromo-compound (6 g.) was reduced in methyl alcohol (50 c.c.) over palladised charcoal (0·5 g.), yielding tetronic acid as sticky solid, which was crystallised from water, giving the pure acid (2 g.), m. p. 139—140° (softens at 136°).

α-Methyltetronic acid had m. p. 190—191° (cf. Freer, *loc. cit.*), $\lambda_{max.}$ 2315 Å (log ε 4·09), absorption max. at 1758 (in $CH_2Cl{\cdot}CH_2Cl$), 1751, and 1676 cm.$^{-1}$ (in $CHCl_3$) (Found : C, 52·6; H, 5·3. Calc. for $C_5H_6O_3$: C, 52·6; H, 5·3%).

α-Ethyltetronic acid, prepared by a similar method from ethyl α-ethylacetoacetate (40 g.),

crystallised from water as needles (10 g.), m. p. 126°, $\lambda_{max.}$ 2330 Å (log ε 4·12) in HCl–EtOH (Found: C, 55·9; H, 6·1. Calc. for $C_6H_8O_3$: C, 56·25; H, 6·25%).

Ethyl α-propionylpropionate (10 g.) similarly gave *αγ-dimethyltetronic acid* (2·5 g.) which crystallised from water as needles, m. p. 120—121°, $\lambda_{max.}$ 2310 Å (log ε 3·998) in EtOH, absorption bands at 1756, 1690 (in $CH_2Cl{\cdot}CH_2Cl$), 1738, 1673 (in $CHCl_3$), 1725, 1664, and 2720 cm.$^{-1}$ (in Nujol) (Found: C, 56·1; H, 6·1. $C_6H_8O_3$ requires C, 56·25; H, 6·25%).

	(XVII; R=R′=H)	(XVII; R=Me, R′=H)	(XVII; R=R′=Me)	(XVII; R=Et, R′=H)	Et·CO·CHMe·CO_2Me
Fe^{+++} reaction ...	Orange-red	Violet-red	Red	Red	Violet
CHI_3 reaction (cold)	−	+	+	−	+
Reduction of Tollens's reagent ...	−	−	−	−	+
Reduction of Fehling's soln.	−	−	−	−	+
Reaction with $NaHCO_3$	+	+	+	+	−
p*K* (water) (±0·1)	3·6	3·6	4·0	4·0	

	Et·CO·CHMe·COEt	Ph·CO·CH_2·COPh	Ph·CO·CHMe·COPh	Ph·C(OH):CMe·COPh
Fe^{+++} reaction ...	Violet	Violet	—	Violet
CHI_3 reaction (cold)	+	−	−	+
Reduction of Tollens's reagent ...	+	−	−	−
Reduction of Fehling's soln.	+	−	−	−
Reaction with $NaHCO_3$	−	−	−	−
p*K* (water) (±0·1)				

	Pr^n·CO·CHEt·CO_2Me	Ph·CO·CHEt·COPh	A	B	C
Fe^{+++} reaction ...	Red	−	−	−	−
CHI_3 reaction (cold)	−	−	++	++	++
Reduction of Tollens's reagent ...	−	−	++	++	++
Reduction of Fehling's soln.	−	−	++	++	++
Reaction with $NaHCO_3$	−	−	−	−	−
p*K* (water) (±0·1)			*	7·0	

* No p*K* value obtainable since the change A ⟶ B takes place even in weak alkali. ++ = Rapid reaction. − = No reaction.

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*Triterpenoids. Part XXXII.** cyclo*Laudenol, a Triterpenoid Alcohol from Opium.*

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From the alkaloid-free fraction of opium (+)-*n*-nonacosan-10-ol and a new triterpenoid alcohol, named *cyclo*laudenol, have been isolated. *cyclo*-Laudenol contains a vinylidene group and a *cyclo*propane ring. The reactions of the dihydro-derivative, *cyclo*laudanol, are very similar to those of *cyclo*-artanol, this similarity extending to molecular-rotation relations. It is concluded that *cyclo*laudenol and *cyclo*artenol have the same nuclear structure and differ only in the nature of their side chains.

Opium has been the subject of chemical examination since the beginning of the eighteenth century and approximately thirty different alkaloids have been isolated from this source and their structures elucidated. The commercial extraction of alkaloids from opium has achieved a high level of efficiency although the method employed is believed to be essentially that described in 1833 by Gregory (*Annalen*, **7**, 261; cf. Anderson, *ibid.*, 1853, **86**, 180). The opium is stirred with water, the mixture treated with a hot solution of calcium chloride and filtered, and the press-cake washed. The filtrate and washings are combined and processed for alkaloids. The press-cake has been shown to contain the calcium salts of meconic, lactic, and sulphuric acids, but apart from this observation there is no record of an examination of the non-alkaloidal constituents of opium.

Through the courtesy of the Directors of Messrs. T. and H. Smith Ltd., Edinburgh, we have been able to examine the press-cake or marc from opium. Extraction of the marc with chloroform gave a fat (18%), which was saponified by using alcoholic potassium hydroxide. The non-saponifiable fraction was obtained as an orange-coloured gum which, not without difficulty, was crystallised from acetone. The crystalline solid was chromatographed on alumina, the most easily eluted fraction being a gum which has not been examined. The next fraction was a crystalline, optically inactive alcohol, $C_{29}H_{60}O$, m. p. 81—82°, which gave negative reactions in the Liebermann–Burchard test and with the tetranitromethane reagent. The alcohol was characterised as its acetate, and was oxidised to the corresponding ketone, reduction of which by the Wolff–Kishner method gave a hydrocarbon, $C_{29}H_{60}$. The analytical data and physical constants of the alcohol and its derivatives suggested that it is (+)-*n*-nonacosan-10-ol. This alcohol was isolated by Chibnall, Piper, Pollard, Smith, and Williams (*Biochem. J.*, 1931, **25**, 2095) from apple cuticle wax; it does not show any appreciable optical rotation although the hydrogen phthalate has a very slight dextrorotation. (+)-*n*-Nonacosan-10-ol has also been isolated from the fruit of *Ginkgo bilboa* (Kawamura, *Jap. J. Chem.*, 1928, **3**, 89; Chibnall and Piper, *Biochem. J.*, 1934, **28**, 2209). A comparison of the m. p.s of the alcohol and its derivatives isolated from the three sources is shown below:

	Opium	Apple cuticle	*Ginkgo bilboa*
(+)-*n*-Nonacosan-10-ol	81—82°	81·9—82·2°	82·5°
(+)-*n*-Nonacosan-10-yl acetate	44·5—45·5	44·5—45	43—43·5
n-Nonacosan-10-one	74·5—75·5	74·7—74·9	74
n-Nonacosane	63—64	62·7—63	—

The alcohol obtained from opium and its acetate and ketone were undepressed in m. p. when mixed with the corresponding compounds derived from apple cuticle wax and kindly given to us by Professor A. C. Chibnall, F.R.S., to whom we express our best thanks. The infra-red absorption spectra of the alcohols from the two sources were identical.

Continued elution of the alumina column gave a principal fraction from which an alcohol was readily isolated and characterised by preparation of a number of derivatives.

* The Paper by McKean and Spring, *J.*, 1954, 1989, is considered to be Part XXXI.

In the Liebermann–Burchard test the alcohol gives a deep red solution with a strong green fluorescence. Because of its origin and for reasons which emerge below, we name this alcohol *cyclo*laudenol. Analyses of the alcohol and its derivatives did not allow a firm decision to be made between the formulæ $C_{30}H_{50}O$, $C_{31}H_{52}O$, and $C_{32}H_{54}O$ for the parent.

The presence of a secondary hydroxyl group in *cyclo*laudenol follows from the preparation of an acetate and a benzoate and from its oxidation to a ketone, *cyclo*laudenone, which is stable to chromic acid at room temperature. A number of observations show that *cyclo*laudenol contains one double bond which is reactive. First, when shaken over a platinum catalyst, *cyclo*laudenyl acetate absorbs one mol. of hydrogen to yield *cyclo*laudanyl acetate. Secondly, the first acetate absorbs one mol. of bromine to yield its dibromide, and finally, oxidation of *cyclo*laudenyl acetate with perbenzoic acid yields a monoxide. As expected from this behaviour, *cyclo*laudenyl acetate shows an apparent absorption maximum at 2060 Å ($\varepsilon = 1500$) whereas *cyclo*laudanyl acetate and *cyclo*laudenyl acetate oxide do not show any appreciable absorption in the ethylenic region. In contrast to their apparently saturated nature, however, *cyclo*laudanyl acetate, the derived *cyclo*laudanol, *cyclo*laudenyl acetate oxide, and *cyclo*laudenyl acetate dibromide each give a faint but distinct colour with tetranitromethane.

A close relation between *cyclo*laudenol and *cyclo*artenol (I) (Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673; Henry and Spring, *Chem. and Ind.*, 1954, 189; Barton, Page, and Warnhoff, *J.*, 1954, 2715) was suggested at an early stage in this work by a number of considerations. First, dihydro-derivatives of both compounds do not show light absorption in the ethylenic region but do give a positive reaction with the tetranitromethane reagent. Secondly, molecular-rotation differences between corresponding compounds of both series are similar, as shown in the following Table, and in particular

	M_D *						
	Alcohol	Acetate	Benzoate	Ketone	Δ_1	Δ_2	Δ_3
*cyclo*Artenol	+230°	+280°	+400°	+ 93°	+50°	+170°	−137°
*cyclo*Laudenol	+266	+265	+343	+ 83	+59	+137	−123
*cyclo*Artanol	+214	+277	—	+102	+63	—	−112
*cyclo*Laudanol	+190	+242	—	—	+52	—	—

* The M_D values for *cyclo*laudenol and its derivatives given in this paper are based on the molecular formula $C_{31}H_{52}O$, as are the theoretical values for carbon and hydrogen analyses.

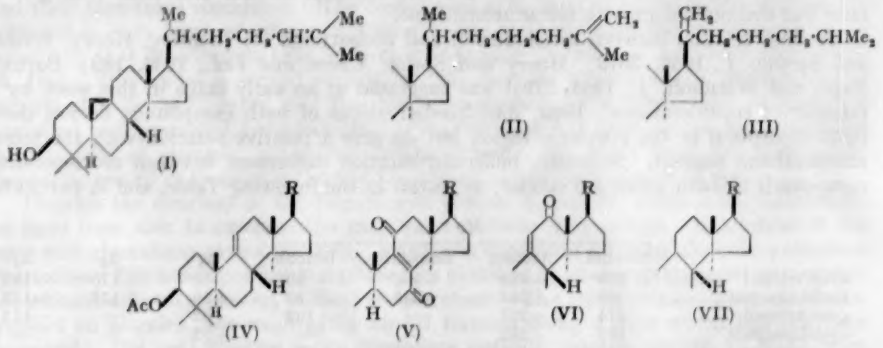
the change in molecular rotation accompanying oxidation of *cyclo*laudenol to *cyclo*laudenone is strongly negative, whereas with many naturally occurring triterpenoid alcohols it is positive. Members of the tetracyclic triterpenoid group containing a reactive double bond show little change in molecular rotation on hydrogenation (Barton and Jones, *J.*, 1944, 659; Jones and Woods, *J.*, 1953, 464). In this respect, *cyclo*laudenol, like *cyclo*artenol, is related to this group. Again, the molecular-rotation change accompanying acetylation of a 3β-hydroxy-triterpenoid is positive, whereas the corresponding change for a 3α-hydroxy-compound is strongly negative (Halsall, Meakins, and Swayne, *J.*, 1953, 4139). The molecular-rotation changes on acetylation of *cyclo*laudenol and *cyclo*laudanol are positive and roughly equal to those observed for *cyclo*artenol and *cyclo*artanol, from which it is inferred that if *cyclo*laudenol resembles *cyclo*artenol in being a 3-hydroxy-triterpenoid, the hydroxyl group has the β-configuration.

The suspected presence of a *cyclo*propane ring in *cyclo*laudenol was confirmed as follows. Treatment of *cyclo*laudanyl acetate with hydrogen chloride gave an acetate mixture, m. p. 145—155°, which in contrast to *cyclo*laudanyl acetate gives a strong yellow colour with tetranitromethane and shows ethylenic absorption between 2000 and 2200 Å. From this mixture, by a tedious crystallisation procedure, a homogeneous compound, laudenyl acetate, m. p. 173—174°, was isolated which shows an apparent absorption maximum at 2080 Å ($\varepsilon = 3000$) and gives a strong yellow colour with the tetranitromethane reagent. The infra-red absorption spectra of *cyclo*laudenol and its derivatives were kindly examined by Dr. A. R. H. Cole, of the University of Western Australia, to whom we express our best thanks. In carbon tetrachloride solution, *cyclo*laudenol, its

acetate, and *cyclo*laudanyl acetate all show a band at 3040 cm.$^{-1}$ characteristic of a methylene group included in a *cyclo*propane ring (Cole, *Chem. and Ind.*, 1953, 946).

Ozonolysis of *cyclo*laudenyl acetate gives formaldehyde and a ketone oxonor*cyclo*laudanyl acetate; thus in contrast to *cyclo*artenol which contains an *iso*propylidene group, *cyclo*laudenol contains a vinylidene group. The presence of a vinylidene group was confirmed by Dr. Cole's infra-red measurements; the spectra of *cyclo*laudenol and its acetate include bands at 3071 cm.$^{-1}$ (in carbon tetrachloride) and at 887 cm.$^{-1}$ (in carbon disulphide) and these bands are absent from the spectrum of *cyclo*laudanyl acetate.

The possibility that *cyclo*laudenol differs from *cyclo*artenol simply in the position of the double bond in the side chain was next considered. If *cyclo*laudenol is (II), *cyclo*laudanyl acetate should be identical with *cyclo*artanyl acetate (VII; R = C_8H_{17}) whereas the two are distinct. If *cyclo*laudenol is (III), the non-identity of *cyclo*artanyl acetate (VII; R = C_8H_{17}) and *cyclo*laudanyl acetate requires that hydrogenation of the $\Delta^{20\,(21)}$-bond in *cyclo*laudenyl acetate has proceeded quantitatively to give the unnatural configuration at $C_{(20)}$. This point will be further discussed in a later paper dealing with a closer investigation of the side chain of *cyclo*laudenol.



Attention was next directed to the preparation of the parent tetracyclic alcohol, laudanol, and its derivatives. The preparation of laudenyl acetate by direct crystallisation of the mixture obtained by hydrogen chloride isomerisation of *cyclo*laudanyl acetate is accompanied by considerable losses. Application of the method previously described for the preparation of lanost-9(11)-enyl acetate (IV; R = C_8H_{17}) from the mixture obtained by treatment of *cyclo*artanyl acetate with hydrogen chloride (Bentley, Henry, Irvine, and Spring, *loc. cit.*) was more efficient. Treatment of the acetate mixture, m. p. 145—155°, with chromic acid under mild conditions, followed by chromatography, gave three homogeneous compounds. The most easily eluted was laudenyl acetate identical with that obtained by direct crystallisation of the mixture, m. p. 145—155°. A second product is a yellow acetate, m. p. 186°, analysis of which agrees with the molecular formula $C_{33}H_{52}O_4$ (or a near homologue). It does not give a colour with tetranitromethane and shows the characteristic ultra-violet absorption spectrum of a fully transoid $\overset{|}{C}O\text{–}\overset{|}{C}\text{=}\overset{|}{C}\text{–}\overset{|}{C}O$ system, with a maximum at 2700 Å (ε = 7400). This compound is an analogue of 7 : 11-dioxolanost-8-enyl acetate (V; R = C_8H_{17}) and, like the latter, it is reduced by zinc dust and acetic acid to a saturated diketone. The third product of the reaction was isolated in only small yield; analysis supported the formula $C_{33}H_{54}O_3$ (or a near homologue). It does not give a colour with tetranitromethane and shows the ultra-violet absorption spectrum of an $\alpha\beta$-unsaturated ketone with a maximum at 2410 Å (ε = 11,400). It is an analogue of 12-oxolanost-9(11)-enyl acetate (VI; R = C_8H_{17}) and it is obtained in high yield by oxidation of laudenyl acetate with chromic acid.

Catalytic hydrogenation of the acetate mixture, m. p. 145—155°, obtained from *cyclo*laudanyl acetate by treatment with hydrochloric acid, and treatment of the mixture

with chromic acid, followed by chromatography, gave the saturated laudanyl acetate as major product and dioxolaudenyl acetate as minor product. From laudanyl acetate, laudanol, laudanone, and laudane were prepared by standard methods.

The reactions of *cyclo*laudanol described above exactly parallel those of *cyclo*artanol and this striking similarity extends to the molecular-rotation relations of corresponding derivatives, as shown in the following Table. As a consequence of this exact parallelism,

	M_D				
	Alcohol	Acetate	Ketone	Δ_1	Δ_2
Laudanol	+ 93°	+155°	+ 62°	+62°	−31°
Lanostanol (artanol)	+150	+193	+116	+43	−34

Acetate	M_D	Δ [a]	Acetate	M_D	Δ [b]
Laudanyl	+155°	—	Lanostanyl	+193°	—
*cyclo*Laudanyl	+242	+ 87°	*cyclo*Artanyl	+247	+ 54°
Laudenyl	+387	+232	Lanost-9(11)-enyl	+400	+207
Oxolaudenyl	+434	+279	12-Oxolanost-9(11)-enyl	+440	+247
Dioxolaudenyl	+364	+209	7 : 11-Dioxolanost-8-enyl	+460	+267
Dioxolaudanyl	+257	+102	7 : 11-Dioxolanostanyl	+320	+127

[a] Δ Value is M_D (derivative)—M_D (laudanyl acetate). [b] Δ Value is M_D (derivative)—M_D (lanostanyl acetate).

we provisionally conclude that *cyclo*laudenol has the same nuclear structure as *cyclo*artenol and that the two alcohols differ solely in the nature of the side chain.

Experimental

Specific rotations were measured in chloroform solution in a 1-dm. tube at room temperature, and ultra-violet absorption spectra were measured in ethanol solution by use of a Unicam SP.500 spectrophotometer. Grade II alumina and light petroleum of b. p. 60—80° were used for chromatography unless otherwise specified.

Non-saponifiable Fraction of Opium Marc.—Opium marc (1 kg.) was extracted with boiling chloroform (2 × 4 l.), the combined extracts were evaporated, and the residue was dissolved in ether (4 l.) and washed with 3N-hydrochloric acid. The brown gum (180 g.), obtained on removal of solvent, was extracted with a mixture of boiling benzene (300 ml.) and ethanol (2 l.), and the extract decanted from a rubber-like material (10 g.). The extract was refluxed with a saturated solution of potassium hydroxide (120 g.) for 3 hr. The non-saponifiable fraction (43 g.) was isolated by means of ether in the usual manner. A solution of the non-saponifiable fraction in acetone (100 ml.) was kept at room temperature, and the crystalline solid separating (18·5 g.) was collected. A second crop (2·5 g.) was obtained by keeping the mother-liquor at room temperature. The acetone-soluble fraction of the non-saponifiable fraction of opium has not been examined in detail.

(+)-n-*Nonacosan*-10-*ol*.—A solution of the crystalline solid (21 g.) in benzene (500 ml.) was percolated through a column (4·5 × 32 cm.) of alumina (520 g.), and the chromatogram eluted with (*a*) benzene (4·1), (*b*) benzene–ether (19 : 1; 6 l.), (*c*) benzene–ether (19 : 1; 2·5 l.), (*d*) benzene–ether (9 : 1; 9 l.), (*e*) benzene–ether (4 : 1; 4·5 l.), (*f*) benzene–ether (1 : 1; 3 l.), (*g*) benzene–ether (1 : 1; 4·5 l.), and (*h*) benzene–methanol (9 : 1; 1·5 l.). Evaporation of solution (*b*) gave a solid (3·2 g.) which when crystallised from ethyl acetate yielded (+)-*n*-nonacosan-10-ol as prisms, m. p. 81—82°, $[\alpha]_D$ ±0° (*c*, 2·5) (Found: C, 81·8; H, 14·2. Calc. for $C_{29}H_{60}O$: C, 82·0; H, 14·2%).

(+)-*n*-Nonacosan-10-yl acetate, prepared from the alcohol by using acetic anhydride and pyridine, separated from ethyl acetate as plates, m. p. 44·5—45·5° (Found: C, 79·6; H, 13·3. Calc. for $C_{31}H_{62}O_2$: C, 79·8; H, 13·4%).

n-*Nonacosan*-10-*one*.—A solution of (+)-*n*-nonacosan-10-ol (500 mg.) in acetic acid (100 ml.) was treated at 50° with a solution of chromic acid (110 mg.) in acetic acid (25 ml.), during 30 min. After 16 hr. at room temperature, methanol (5 ml.) was added, and the product isolated by means of ether. Crystallisation from ethyl acetate gave *n*-nonacosan-10-one as plates (427 mg.), m. p. 74·5—75·5° (Found: C, 82·4; H, 14·0. Calc. for $C_{29}H_{58}O$: C, 82·4; H, 13·8%).

n-*Nonacosane*.—A mixture of *n*-nonacosan-10-one (225 mg.), hydrazine hydrate (100%, 2 ml.), and a solution of sodium ethoxide (from 250 mg. of sodium) in absolute ethanol (15 ml.)

was kept at 200—210° for 18 hr. The product, isolated in the usual manner, crystallised from ethyl acetate as plates (186 mg.), m. p. 63—64° (Found: C, 84·8; H, 14·8. Calc. for $C_{30}H_{60}$: C, 85·2; H, 14·8%).

cyclo*Laudenol*.—Evaporation of the combined fractions (*c*)—(*f*) from the chromatogram gave a gum (12·4 g.) which readily crystallised from methanol to yield cyclo*laudenol* as needles (6 g.), m. p. 125°, $[\alpha]_D$ +46° (*c*, 1·5) (Found: C, 84·6, 84·4; H, 11·9, 12·1. $C_{31}H_{52}O$ requires C, 84·5; H, 11·9%). The alcohol gives a pale yellow colour with the tetranitromethane reagent. Light absorption: Max. at 2050 Å ($\varepsilon = 1145$). In the Liebermann–Burchard test *cyclo*laudenol gives a blood-red solution with a strong green fluorescence.

*cyclo*Laudenol (250 mg.), acetic anhydride (5 ml.), and pyridine (10 ml.) for 12 hr. at room temperature gave the *acetate*, which separates from chloroform–methanol as blades, m. p. 120—121°, $[\alpha]_D$ +55° (*c*, 1·5) (Found: C, 82·3; H, 11·5. $C_{33}H_{54}O_2$ requires C, 82·1; H, 11·3%).

*cyclo*Laudenol (400 mg.) in pyridine (5 ml.) was heated with benzoyl chloride (1 ml.) for 1½ hr. The *benzoate* crystallised from chloroform–methanol as needles, m. p. 194—195°, $[\alpha]_D$ +63° (*c*, 0·9) (Found: C, 83·5; H, 10·5. $C_{38}H_{56}O_2$ requires C, 83·8; H, 10·4%). Hydrolysis with 5% ethanolic potassium hydroxide gave *cyclo*laudenol, m. p. and mixed m. p. 125°, $[\alpha]_D$ +45° (*c*, 1·0).

cyclo*Laudenone*.—A solution of *cyclo*laudenol (460 mg). in acetic acid (100 ml.) was stirred at room temperature, and chromic acid (95 mg.) in acetic acid (20 ml.) added during 30 min. Next morning the neutral product was isolated in the usual way, and crystallised from methanol to yield cyclo*laudenone* as blades (285 mg.), m. p. 115°, $[\alpha]_D$ +19° (*c*, 1·3) (Found: C, 84·3; H, 11·6. $C_{31}H_{50}O$ requires C, 84·9; H, 11·5%).

cyclo*Laudanyl Acetate*.—*cyclo*Laudenyl acetate (500 mg.) in glacial acetic acid (150 ml.) was shaken with hydrogen and platinum (from 300 mg. of platinum oxide) for 30 min., absorption of hydrogen then having ceased. The product was crystallised from chloroform–methanol to give cyclo*laudanyl acetate* as needles (440 mg.), m. p. 132—133°, $[\alpha]_D$ +50° (*c*, 0·8) (Found: C, 81·8; H, 11·7. $C_{33}H_{56}O_2$ requires C, 81·8; H, 11·6%). It gives a pale yellow colour with tetranitromethane and shows no selective light absorption between 2000 and 2250 Å. Hydrolysis of *cyclo*laudanyl acetate with 3% ethanolic potassium hydroxide gave cyclo*laudanol*, which separates from methanol as needles, m. p. 133—134°, $[\alpha]_D$ +43° (*c*, 0·9) (Found: C, 83·9; H, 12·1. $C_{31}H_{54}O$ requires C, 84·1; H, 12·3%).

*Epoxy*cyclo*laudanyl Acetate*.—*cyclo*Laudenyl acetate (500 mg.) in chloroform (10 ml.) was treated at 0° with a chloroform solution of perbenzoic acid (1·7 ml., 106 mg./ml., 1·2 mol.). After 24 hr. at 0°, the product was isolated and twice crystallised from methanol to yield *epoxy*cyclo*laudanyl acetate*, as needles (336 mg.), m. p. 153—154°, $[\alpha]_D$ +54° (*c*, 1·8) (Found: C, 79·0; H, 10·9. $C_{33}H_{54}O_3$ requires C, 79·5; H, 10·9%).

cyclo*Laudenyl Acetate Dibromide*.—A solution of bromine in acetic acid (7·5 ml.; 15·1 mg./ml.; 1·1 mol.) was added to *cyclo*laudenyl acetate (300 mg.) in acetic acid at room temperature. The product separated as needles (210 mg.), m. p. 170—171° (decomp.). Crystallisation from chloroform–methanol gave the *dibromide* as needles, m. p. 179—180° (decomp.), $[\alpha]_D$ +38° (*c*, 1·0); the analysis was not satisfactory (Found: C, 62·7; H, 8·7. $C_{33}H_{54}O_2Br_2$ requires C, 61·7; H, 8·5%).

Ozonolysis of cyclo*Laudenyl Acetate*.—*cyclo*Laudenyl acetate (3 g.) in dry chloroform (150 ml.) was treated at −45° with ozonised oxygen (2 mols. of ozone) for 30 min. After attaining room temperature, the solution was treated with acetic acid (25 ml.), and portionwise with zinc dust (6 g.) during 30 min. with stirring. After 1 hour's stirring, the filtered solution was washed with water. The aqueous washings were combined, adjusted to pH 7·0, and treated with a saturated aqueous solution of dimedone (200 ml.). After 24 hr. at 0° the separated formaldehyde–dimedone compound (0·64 g., 35%) was collected and crystallised from ethanol, from which it separated as needles, m. p. and mixed m. p. 189—190° (Found: C, 69·5; H, 8·4. Calc. for $C_{17}H_{24}O_4$: C, 69·8; H, 8·3%). Evaporation of the dried chloroform solution gave a solid which was dissolved in light petroleum (200 ml.) and percolated through a column (2·75 × 18 cm.) of alumina (90 g.). Elution with light petroleum (1000 ml.) and light petroleum–benzene (3 : 1; 1400 ml.) gave a fraction (2·0 g.) which, after crystallisation from methanol, gave *oxonor*cyclo*laudanyl acetate* as needles, m. p. 140—141°, $[\alpha]_D$ +61° (*c*, 1·3) (Found: C, 79·2; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). The *oxime* separated from methanol as needles, m. p. 160—161°, $[\alpha]_D$ +54° (*c*, 0·8) (Found: C, 77·0; H, 10·6. $C_{32}H_{53}O_3N$ requires C, 76·9; H, 10·7%).

Treatment of cyclo*Laudanyl Acetate with Hydrogen Chloride*.—A solution of the acetate (1 g.) in dry chloroform (50 ml.) at 0° was treated with a stream of dry hydrogen chloride

for 3 hr. The product, isolated in the usual manner, crystallised from chloroform–methanol as needles (770 mg.), m. p. 145—155°, $[\alpha]_D$ +62° (*c*, 1·5), showing a strong yellow colour with tetranitromethane. Light absorption: Max. at 2080 Å (ε = 3100).

Laudenyl Acetate.—(i) Six crystallisations of the acetate mixture, m. p. 145—155° (770 mg.), described above, from chloroform–methanol gave *laudenyl acetate* as needles (60 mg.), m. p. 173—174°, $[\alpha]_D$ +81° (*c*, 0·9) (Found: C, 81·4; H, 11·5. $C_{33}H_{56}O_2$ requires C, 81·8; H, 11·6%). Light absorption: Max. at 2060 Å (ε = 3100).

(ii) Chromic acid (440 mg.) in 90% acetic acid (25 ml.) was added during 5 min. to a solution of the acetate mixture, m. p. 145—155° (1·47 g.), in acetic acid (100 ml.) at 90°. The mixture was heated for a further 10 min. and diluted with water, and the product (1·46 g.) isolated by means of ether. A solution of this solid in light petroleum (100 ml.) was filtered through a column (2 × 16 cm.) of alumina (45 g.), and the chromatogram eluted with (*a*) light petroleum (1·1 l.), (*b*) light petroleum–benzene (4 : 1; 1·3 l.), (*c*) light petroleum–benzene (1 : 1; 600 ml.), (*d*) benzene (200 ml.), and (*e*) benzene (500 ml.). Fraction (*a*) (610 mg., m. p. 171—173°) was twice crystallised from chloroform–methanol to give laudenyl acetate, m. p. 173°, $[\alpha]_D$ +80° (*c*, 1·4) (Found: C, 81·8; H, 11·9%). A mixture with the specimen obtained by method (i) was undepressed in m. p.

Dioxolaudenyl Acetate.—Fraction (*c*) from the chromatogram described above was evaporated. The yellow crystalline solid (270 mg., m. p. 184—185°) was crystallised from methanol to give *dioxolaudenyl acetate* as light yellow blades, m. p. 186°, $[\alpha]_D$ +71° (*c*, 1·1) (Found: C, 77·0; H, 10·5. $C_{33}H_{58}O_4$ requires C, 77·3; H, 10·2%). Light absorption: Max. at 2700 Å (ε = 7400).

Oxolaudenyl Acetate.—(i) Chromic acid (300 mg.) in acetic acid was added during 1 hr. to a refluxing solution of laudenyl acetate (300 mg.) in acetic acid (50 ml.), and heating continued for 2 hr. The neutral product, isolated by means of ether, in light petroleum (25 ml.) was filtered through a column (1 × 14 cm.) of alumina (9 g.). Elution with light petroleum (125 ml.) gave a fraction, crystallisation of which from methanol yielded laudenyl acetate in blades (30 mg.), m. p. and mixed m. p. 171—172°. Elution with light petroleum–benzene (1 : 1; 150 ml.), benzene (75 ml.), and benzene–ether (4 : 1; 75 ml.) gave a fraction 130 mg.), which after several crystallisations from methanol yielded *oxolaudenyl acetate* as blades, m. p. 194°, $[\alpha]_D$ +87° (*c*, 0·9) (Found: C, 80·0; H, 10·9. $C_{33}H_{54}O_3$ requires C, 79·5; H, 10·9%). Light absorption: Max. at 2410 Å (ε = 10,300).

(ii) Fraction (*e*) from the chromatogram used in the preparation of laudenyl acetate was evaporated, and the solid (m. p. 188—189°, 120 mg.) twice crystallised from methanol to give oxolaudenyl acetate as blades, m. p. 188—189°, $[\alpha]_D$ +85° (*c*, 1·4), undepressed in m. p. when mixed with the specimen described above.

Dioxolaudanyl Acetate.—Zinc dust (1 g.) was added portionwise to a refluxing solution of dioxolaudenyl acetate (50 mg.) in acetic acid (10 ml.), and refluxing continued for 1 hr. The product, isolated by means of ether, crystallised from methanol to give *dioxolaudanyl acetate* as plates (34 mg.), m. p. 241°, $[\alpha]_D$ +50·5° (*c*, 1·5) (Found: C, 77·2; H, 10·7. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·6%).

Laudanyl Acetate.—A solution of the acid-isomerisation mixture from *cyclo*laudanyl acetate (m. p. 145—155°, 3·2 g.) in glacial acetic acid (300 ml.) was shaken at 80° for 7 hr. with hydrogen and platinum (1·5 g.). The product crystallised from chloroform–methanol as needles (2·1 g.), m. p. 153—156°, $[\alpha]_D$ +35° (*c*, 1·3). A solution of this mixture in acetic acid (300 ml.) was treated on the steam-bath with a solution of chromic acid (1·2 g.) in acetic acid (75 ml.) added during 30 min. The mixture was heated for 1 hr., the neutral product (2·0 g.) isolated in the usual manner and dissolved in light petroleum (150 ml.), and the solution percolated through a column (2·25 × 16 cm.) of alumina (60 g.). Elution with light petroleum (1500 ml.) gave *laudanyl acetate* (600 mg.) which separated as needles from chloroform–methanol, m. p. 171°, $[\alpha]_D$ +32° (*c*, 1·2) (Found: C, 81·2; H, 12·3. $C_{33}H_{56}O_2$ requires C, 81·4; H, 12·0%). Elution with light petroleum–benzene (4 : 1; 450 ml.) yielded a fraction (170 mg.) which separated as pale yellow needles from methanol, m. p. 183—184°, alone or mixed with dioxolaudenyl acetate, $[\alpha]_D$ +67·5° (*c*, 0·6). Light absorption: Max. at 2720 Å (ε = 6900).

Laudanol.—Hydrolysis of laudanyl acetate in 3% ethanolic potassium hydroxide followed by crystallisation of the product from chloroform–methanol yielded *laudanol* as fine needles, m. p. 200—201°, $[\alpha]_D$ +21° (*c*, 0·9) (Found: C, 84·0; H, 12·8. $C_{31}H_{54}O$ requires C, 83·7; H, 12·7%).

Laudanone.—Oxidation of laudanol (500 mg.) with chromic acid (100 mg.) in acetic acid (20 ml.) for 12 hr. at room temperature and isolation of the neutral product in the usual

manner, gave *laudanone* (360 mg.), which separated as plates from chloroform–methanol, m. p. 131—132°, $[\alpha]_D$ +14° (*c*, 1·0) (Found: C, 84·1; H, 12·5. $C_{21}H_{34}O$ requires C, 84·1; H, 12·3%).

Laudane.—A mixture of laudanone (200 mg.), hydrazine hydrate (100%, 2 ml.), and sodium ethoxide (from 250 mg. of sodium) in ethanol (10 ml.) was kept at 200° for 18 hr. A solution of the dried product, isolated by means of ether, in light petroleum (25 ml.) was filtered through a column (1 × 9 cm.) of alumina (6 g.). Elution with light petroleum (50 ml.) gave a fraction (145 mg.) which after crystallisation from chloroform–methanol yielded *laudane* as plates, m. p. 142—143°, $[\alpha]_D$ +25° (*c*, 1·7) (Found: C, 87·0; H, 13·2. $C_{21}H_{36}$ requires C, 86·8; H, 13·2%).

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Some Complex Oxyfluorides of Septavalent Rhenium.

By R. D. PEACOCK.

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Bromine trifluoride reacts with metallic per-rhenates to form complex oxyfluorides of septavalent rhenium, of general formula $M^{I}ReO_2F_4$ and $M^{II}(ReO_2F_4)_2$. Complete substitution of fluorine for oxygen leading to oxygen-free compounds does not take place under the conditions employed.

ALTHOUGH oxyfluoride complexes of molybdenum and tungsten are well known (cf. Sidgwick, "The Chemical Elements and their Compounds," Vol. II, p. 1044) none of rhenium has been described. Ruff and Kwasnik (*Z. anorg. Chem.*, 1934, **219**, 65) and also Wiechert (*ibid.*, 1950, **268**, 310) observed residues containing potassium, rhenium, oxygen, and fluorine, but in neither case was a definite compound isolated. Aynsley, Peacock, and Robinson (*J.*, 1950, 1622), using fluorine itself on potassium per-rhenate, obtained only the two volatile oxyfluorides, rhenium dioxytrifluoride ReO_2F_3 and oxypentafluoride $ReOF_5$, leaving a residue of potassium fluoride. In the present investigation bromine trifluoride has been used as the fluorinating agent (cf. Sharpe, *J.*, 1950, 3444), more particularly in view of the successful preparation of complex fluorides of some of the platinum metals (cf. Hepworth, Peacock, and Robinson, *J.*, 1954, 1197) by this means.

Potassium per-rhenate reacts quietly with bromine trifluoride at room temperature; oxygen and bromine are evolved and warming gives a clear yellow solution which, after the solvent has been pumped off, yields a cream-coloured solid. This is potassium tetrafluoroper-rhenate, $KReO_2F_4$; being very hygroscopic, it can only be kept in a dry atmosphere. Its dissolution in water appears soon to be followed by hydrolysis since the initial yellow colour is soon lost, and the colourless liquid gives the reactions of fluoride, per-rhenate, and potassium ions only: $KReO_2F_4 + 2H_2O \longrightarrow K^+ + 2H^+ + ReO_4^- + 2HF_2^-$. The hydrolysis is greatly accelerated by alkali, which immediately decolorizes the solution.

Replacement of potassium by rubidium, cæsium, silver, or barium per-rhenate yields the corresponding complex fluoro-salts $RbReO_2F_4$, $CeReO_4F_4$, $AgReO_2F_4$, and $Ba(ReO_2F_4)_2$, which have similar properties, although the silver salt is darker.

Calcium and strontium per-rhenates, however, are not completely soluble in bromine trifluoride so that pure complex salts were not obtained; further, the residues contained less rhenium than the values calculated for the fluoro-salts, suggesting that the complexes are solvolysed to some extent in bromine trifluoride solution. Sodium per-rhenate is soluble in bromine trifluoride but the product, even after prolonged drying, still contains

bromine. Analysis showed the rhenium content to be low; it is probable that the bromine is present as sodium tetrafluorobromite $NaBrF_4$.

That completely substituted complex fluorides of rhenium are not formed by this method is to be expected; formation of complexes of the type M^IReF_6 as with manganese, or M^IReF_6 as with ruthenium (Hepworth, Peacock, and Robinson, *loc. cit.*), would imply reduction of the stable septavalent state, and no complex salts of the type M^IAF_8 are yet known. The tetrafluoroper-rhenates can be regarded as derivatives of ReO_3F_3 in which the co-ordination number of the rhenium is increased to 6. Other fluorine derivatives of per-rhenates might be expected to exist, *e.g.*, $M^I_2ReO_3F_3$ and $M^I_2ReO_4F_2$, but attempts to prepare one or both of these series by fusion of per-rhenates with potassium hydrogen difluoride, KHF_2, at 250° have been unsuccessful.

Experimental

Metallic per-rhenates were prepared by dissolving powdered rhenium metal in dilute hydrogen peroxide to give per-rhenic acid, neutralizing portions of the hot solution with the corresponding metallic carbonate, and then filtering. Potassium, rubidium, cæsium, and silver per-rhenate separated from their respective solutions on cooling, and sodium and the alkaline-earth per-rhenates crystallized on evaporation of their solutions nearly to dryness. Before reaction the salts were dried at 100° in a vacuum.

Bromine trifluoride was prepared from dry bromine by treating the liquid with hydrogen fluoride-free fluorine suitably diluted with nitrogen, the Pyrex reaction vessel being cooled to 0° in an ice-bath. The crude product was purified by distillation and fractionation in a vacuum.

Potassium per-rhenate reacted immediately with bromine trifluoride at room temperature; the mixture became warm. After evolution of bromine and oxygen had nearly ceased, the remaining solid was dissolved in the bromine trifluoride by warming, and the reaction completed by boiling the solution for 5 min. This solution deposited a quantity of a yellow solid on cooling, which, when the excess of bromine trifluoride had been pumped off at room temperature, appeared as a cream-coloured residue. It was gradually heated to 200° in a vacuum, and after about 30 min. at this temperature, when no more bromine trifluoride could be pumped off, proved to be bromine-free *potassium tetrafluoroper-rhenate* $KReO_3F_4$ (Found: K, 11·9; Re, 55·7; F, 23·0. $KReO_3F_4$ requires K, 11·7; Re, 55·9; F, 23·0%). The *rubidium*, *cæsium*, *silver*, and *barium* salts were prepared in a similar manner [Found: Rb, 22·2; Re, 49·3; F, 18·1. $RbReO_3F_4$ requires Rb, 22·5; Re, 49·1; F, 20·0%. Found: Cs, 31·2; Re, 43·1; F, 18·1. $CsReO_3F_4$ requires Cs, 31·1; Re, 43·6; F, 17·8%. Found: Ag, 26·2; Re, 46·8; F, 18·7. $AgReO_3F_4$ requires Ag, 26·2; Re, 46·3; F, 18·9%. Found: Ba, 18·7; Re, 51·0; F, 21·5. $Ba(ReO_3F_4)_2$ requires Ba, 18·9; Re, 51·3; F, 20·9%].

The calcium and strontium salts were similarly prepared, but the bromine trifluoride solutions were boiled for longer periods in an attempt to bring all the per-rhenate into solution [Found: Re, 55·2; F, 25·3. Calc. for $Ca(ReO_3F_4)_2$: Re, 59·2; F, 24·2%. Found: Re, 56·0; F, 24·0. Calc. for $Sr(ReO_3F_4)_2$: Re, 55·1; F, 22·5%]. In the sodium salt thus prepared, bromine was detected in the residue even after prolonged heating in a vacuum, and its presence in quantity is shown by the observed equivalent weight (Found: Re, 52·1%; equiv., 338. Calc. for $NaReO_3F_4$: Re, 58·7%; equiv., 317·3).

The above materials were analysed, after removal of interfering elements, rhenium as nitron per-rhenate, fluorine as lead chlorofluoride, alkali metals and barium as sulphate, and silver as chloride.

I am indebted to the University of London for a grant for materials, to Messrs. Johnson Matthey and Co., Ltd., for the loan of rhenium, and to Imperial Chemical Industries Limited, General Chemicals Division, for the use of the necessary fluorine cell.

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Oxygen Exchange and the Walden Inversion in sec.*-Butyl Alcohol.*

By C. A. Bunton, (Mrs.) Alicja Konasiewicz, and D. R. Llewellyn.

[Reprint Order No. 5719.]

The rates of oxygen exchange and racemization of an optically active alcohol have been measured for *sec.*-butyl alcohol in aqueous perchloric acid, of up to 1M-concentration. In the range of acid studied the rates of both oxygen exchange and racemization follow the Hammett acidity function, h_0, rather than the stoicheiometric acid concentration. Within the experimental error the overall rate of racemization, at any given acidity, is twice that of oxygen exchange, indicating that every oxygen exchange gives complete inversion of configuration. These results are interpreted in terms of a rate-determining heterolysis of the oxonium ion ($\overset{+}{\text{R}}\text{OH}_2$), in which the incoming water molecule is prevented from entering on the same side as the expelled group and which therefore gives inversion of configuration.

A comparison of the rates of isotopic halide-ion exchange and racemization of some secondary alkyl halides (Hughes, *Trans. Faraday Soc.*, 1938, **34**, 202) proved to be a very powerful tool in the study of the Walden inversion and led to an understanding of this phenomenon in terms of current theories of nucleophilic substitution. In this system the molecularity of the exchange and racemization processes was directly determined from the kinetic form. However, the racemization described in the present work was followed under solvolytic conditions, where the simpler kinetic tests of mechanism are not available.

It has been pointed out by Hammett (" Physical Organic Chemistry," McGraw-Hill, 1940, p. 273—277) that, if the transition state of an acid-catalyzed solvolytic reaction contains the water molecule, the overall rate of that reaction should be proportional to the hydrogen-ion concentration H_3O^+, but that where the water molecule does not intervene in the rate-determining step of the reaction the rate should be proportional to the acidity function h_0, defined as $h_0 = a_{H^+}f_B/f_{BH^+}$, where B is a neutral base. This test of mechanism gives reasonable results in cases in which it has been applied, *viz.*, in the hydrolyses of sucrose and cyanamide and the enolization of *m*-nitroacetophenone (Hammett, *op. cit.*), and in the acid-catalyzed hydrolyses of β- and γ-lactones which have been studied by Long and his co-workers (*J. Amer. Chem. Soc.*, 1950, **72**, 3267; *J. Phys. Chem.*, 1951, **55**, 829).

In the present work the rates of racemization were followed in aqueous perchloric acid up to *ca.* 1M at 100·8°. Typical examples of the kinetic form for individual runs, together with those of oxygen exchange, are tabulated, and the dependence of racemization rate on perchloric acid concentration is shown in Fig. 1, which also gives the corresponding rates for oxygen exchange.

The kinetics of oxygen exchange were followed by two general methods. In the first, *sec.*-butyl alcohol enriched in ^{18}O was prepared by exchange of ethyl methyl ketone with $H_2{}^{18}O$, and reduction of the ketone with lithium aluminium hydride. In any given exchange run the increase in the ^{18}O content of the water was followed with time. In the second method the increase of the isotopic abundance of initially isotopically normal *sec.*-butyl alcohol in enriched water was followed. The alcohol was isolated as an azeotrope with toluene, and its ^{18}O content determined by pyrolysis to carbon monoxide, and mass-spectrometric analysis of this gas. Results of typical runs are shown in tabulated form in the Experimental section, and the dependence of exchange rate on perchloric acid concentration is shown in Fig. 1.

Two salient points emerge from these results. First, neither racemization nor exchange rates follow the hydrogen-ion concentration above the range where it diverges from the acidity function, but both follow the acidity function (Fig. 2). Secondly, the rate of racemization is always twice the rate of oxygen exchange, within the experimental error of the measurement. This latter result implies that every act of substitution gives complete inversion of configuration: $(+)\text{-ROH} + H_2{}^{18}O \longrightarrow (-)\text{-R}^{18}\text{OH} + H_2O$.

The form of the acid catalysis indicates an S_N1 reaction [see equation (2)] and not an S_N2 reaction because the dependence of reaction rate on the acidity function proves that a water molecule does not enter stoicheiometrically into the kinetic expression for the velocity of the substitution reaction. In other words, the bimolecular sequence

$$H_2O + C_4H_9\cdot\overset{+}{O}H_2 \rightleftharpoons H_2\overset{\delta+}{O}\cdots C_4H_9\cdots\overset{\delta+}{O}H_2 \rightleftharpoons H_2\overset{+}{O}\text{-}C_4H_9 + H_2O \quad . \quad . \quad (1)$$

can be excluded. In the S_N1 reaction the rate-determining step is the heterolysis of the oxonium ion, in which the energy maximum is reached for such a short extension of C–O

FIG. 1.

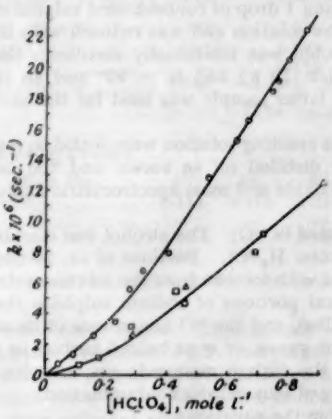
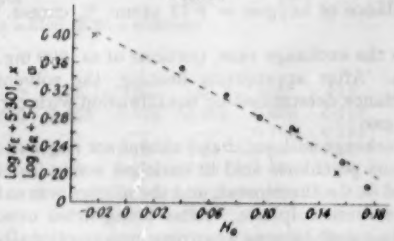


FIG. 2.



bond that the incipiently formed carbonium ion never becomes completely free from the influence of the expelled water molecule, which exerts a shielding effect such that the incoming water molecule always enters from the opposite side.

$$C_4H_9\cdot OH + \overset{+}{H} \rightleftharpoons C_4H_9\cdot\overset{+}{O}H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$\begin{matrix} Me \\ Et \\ H \end{matrix}\!\!>\!C\!-\!\overset{+}{O}H_2 \xrightleftharpoons{\text{slow}} \begin{matrix} Me \\ Et \\ H \end{matrix}\!\!>\!C\overset{\delta+}{\cdots}\overset{\delta+}{O}H_2$$

$$H_2{}^{18}O + \begin{matrix} Me \\ Et \\ H \end{matrix}\!\!>\!C\overset{\delta+}{\cdots}\overset{\delta+}{O}H_2 \xrightleftharpoons{\text{fast}} H_2{}^{18}\overset{+}{O}\!-\!C\!<\!\begin{matrix} Me \\ Et \\ H \end{matrix} + H_2{}^{18}O$$

$$C_4H_9\cdot{}^{18}\overset{+}{O}H_2 \rightleftharpoons C_4H_9\cdot{}^{18}OH + \overset{+}{H}$$

Similar cases of reactions which are of the S_N1 type, since the addition of a reagent (OH^- or OR^-) of a greater nucleophilic power than that of the solvent molecules does not affect the rate, but which give almost complete inversion of configuration are (i) the hydrolysis of *sec.*-butyl hydrogen sulphate, which is independent of pH (Burwell and Holmquist, *J. Amer. Chem. Soc.*, **1948**, **70**, 878) and (ii) the methanolysis of 1-methyl-*n*-heptyl toluene-*p*-sulphonate, where the rate is not highly dependent on methoxide-ion concentration (unpublished results, Bunton and Deschamps). The general phenomenon of steric shielding has recently been discussed by Waters and de la Mare (*Ann. Reports*, **1953**, **50**, 135). In the particular case now discussed there will be a contributing effect in that the proton co-ordinated to the oxygen atom will decrease the local activity of the water molecules in its vicinity and hence impose a restraint on attack of the substituting agent from the direction giving retention of configuration.

Experimental

Resolution.—sec.-Butyl alcohol was resolved *via* the brucine salt of its hydrogen phthalate by the general method of Pickard and Kenyon (*J.*, 1911, **99**, 45). The alcohol obtained from the hydrolysis of the resolved hydrogen phthalate had, after fractional distillation, b. p. 98—99°, n_D^{25} 1·3943, $[\alpha]_D^{18}$ +8·33°.

Kinetics of Racemization.—All runs were carried out in aqueous perchloric acid at 100·8°. At appropriate times the optical activity of portions of the solution was determined at room temperature. The racemization at room temperature was sufficiently slow to allow this procedure to be used.

The acid concentrations quoted are corrected for expansion of the solvent.

Oxygen Exchange.—Preparation of enriched sec.-butyl alcohol. Ethyl methyl ketone (20 g.) was refluxed with *ca.* 30 c.c. of *ca.* 12% $H_2{}^{18}O$ containing 1 drop of concentrated sulphuric acid. The enriched ketone was fractionally distilled from the solution and was reduced with lithium aluminium hydride in dry ether. The enriched alcohol was fractionally distilled; the first fraction (*ca.* 5 g.) had b. p. 98—98·5°, the second (*ca.* 10 g.) had b. p. 99° and an isotope abundance of oxygen = 9·73 atoms % excess. The latter sample was used for the exchange runs.

In the exchange runs, portions of *ca.* 200 mg. of the reacting solution were sealed in separate tubes. After appropriate heating, the solvent was distilled off *in vacuo*, and the isotopic abundance determined by equilibration with carbon dioxide and mass-spectrometric analysis of that gas.

Exchange with sec.-butyl alcohol not originally enriched in ^{18}O. The alcohol was dissolved in aqueous perchloric acid in enriched water (*ca.* 1% excess $H_2{}^{18}O$). Portions of *ca.* 20 c.c. were heated in the thermostat, and the alcohol was extracted with toluene from the solution saturated with sodium sulphate. After being dried over several portions of sodium sulphate the *sec.*-butyl alcohol–toluene azeotrope was fractionally distilled, and the ^{18}O abundance of its alcohol determined by pyrolysis to carbon monoxide over hot gauze, or over heated carbon *in vacuo*. The mass-spectrometric analysis was carried out on the carbon monoxide gas, samples being checked for the presence of argon to preclude possibility of atmospheric contamination.

All the rate coefficients quoted were determined from the equations

for racemization $\log \alpha_0 - \log \alpha = kt/2{\cdot}3$

for oxygen exchange $\log [\beta_\infty/(\beta_\infty - \beta)] = kt/2{\cdot}3$

where β_∞ and β are the isotopic abundances at times ∞ and t, respectively, and t is in sec.

The acidity functions used were interpolated from the values quoted by Hammett *et al.* (*J. Amer. Chem. Soc.*, 1934, **56**, 827). No allowance is made for any variation with temperature, and in the use of this function as a criterion of mechanism we assume the activity of water to be constant in the acidity range considered.

Examples of specimen runs, and the rate constants, are tabulated below, with the concentrations of perchloric acid, and the interpolated values of H_0, where $H_0 = -\log_{10} h_0$. In the racemization runs 1 c.c. of the alcohol was added to 10 c.c. of the perchloric acid in each case. For the exchange runs the concentration of alcohol was varied, and it is therefore tabulated below:

Typical Runs.—Polarimetric run; 100·8°.

Run No. 2R. $[HClO_4]$ = 0·0815M, $NaClO_4$ = 0·217M.

Time (hr.)	0	21·25	43·1	65·75	112·6	138·2	158	181·4
$[\alpha]_D^{18}$	0·294°	0·267°	0·247°	0·220°	0·181°	0·158°	0·143°	0·125°

$10^5 k_1$ = 1·28 sec.$^{-1}$ (obtained graphically).

Exchange runs; 100·8°.

Run No. 19E. $[HClO_4]$ = 0·286M. Isotopically normal *sec.*-butyl alcohol exchanged with $H_2{}^{18}O$ (0·931 atom % excess). Isotopic abundance of alcohol for complete exchange (β_∞) = 0·916 atom % excess.

Time (hr.)	7·9	10·25	15·2	22·33	41·2
β (atom % excess)	0·077	0·105	0·117	0·183	0·267

$10^5 k_1$ = 2·62 sec.$^{-1}$ (obtained graphically).

Run No. 10E. $[HClO_4] = 0{\cdot}690$M. Enriched *sec.*-butyl alcohol ($\beta = 9{\cdot}73$ atom % excess) exchanged with normal water. Isotopic abundance of water for complete exchange (β_∞): Calc., 0·251 atom % excess; found, 0·253, 0·241, 0·256 atom % excess.

Time (hr.)	4·5	6·5	8·5	10·5	16·5	23·5	33
β (atom %) excess	0·0026	0·039	0·053	0·074	0·094	0·122	0·150

$10^5k_1 = 8{\cdot}00$ sec.$^{-1}$ (obtained graphically).

Polarimetric runs:

Run No.	1R	2R *	3R	4R	5R	6R	7R
$[HClO_4]$	0·0408	0·0815	0·164	0·229	0·276	0·319	0·405
H_0	—	—	—	—	—	—	—
10^5k_1 (sec.$^{-1}$)	0·78	1·28	2·53	3·50	5·60	6·80	7·97

Run No.	8R	9R	10R	11R	12R	13R	14R
$[HClO_4]$	0·536	0·628	0·668	0·747	0·769	0·801	0·860
H_0	—	0·175	0·157	0·120	0·107	0·072	0·040
10^5k_1 (sec.$^{-1}$)	12·8	15·3	16·6	18·5	19·2	20·6	22·5

* 0·217M-$NaClO_4$ was added to this solution.

Exchange runs:

Run No.	4E	5E	8E	19E *	17E	16E	18E *	10E	11E	12E *
$[HClO_4]$	0·111	0·176	0·284	0·286	0·432	0·458	0·461	0·690	0·717	0·910
H_0	—	—	—	—	—	—	—	0·152	0·123	−0·025
10^5k_1 (sec.$^{-1}$)	0·67	1·08	3·18	2·62	5·41	4·78	5·94	8·00	9·15	12·5
[Bu^sOH]	1·43	1·40	1·59	1·20	1·06	1·20	2·09	1·16	0·79	0·80

* Runs 12E, 18E, and 19E were carried out with alcohol not originally enriched in ^{18}O.

Formation of Olefin.—Experiments were carried out to decide whether the elimination and subsequent hydration of a butene played any part in the racemizations and exchanges observed. Solutions were aspirated with nitrogen to remove any olefin as fast as it might be formed. The aspirated gases passed through a reflux condenser to a trap at −80°. After a period of time any olefin collected was determined by the addition of excess of bromine, and the estimation of bromine used by iodometry. Two experiments were carried out; in the first the alcohol was heated at 100·8° in 0·4M-aqueous perchloric acid for 6 hr., and in the second with 0·617M-perchloric acid for 6 hr. In both cases the amount of olefin elimination was less than 0·5%.

The authors are indebted to Professors C. K. Ingold, F.R.S., and E. D. Hughes, F.R.S., for their valuable advice on this work, and to Mr. T. A. Lewis for carrying out many of the pyrolyses, all of which were done in apparatus of his design.

William Ramsay and Ralph Forster Laboratories,
University College, London. [*Received, September 10th*, 1954.]

Hydrolytic Decomposition of Esters of Nitric Acid. Part IV. Acid Hydrolysis, and the Effects of Change in the Nucleophilic Reagent on the S_N and E_{CO} Reactions.*

By JOHN W. BAKER and A. J. NEALE.

[Reprint Order No. 5775.]

The rates of solvolysis of ethyl, *iso*propyl, *tert.*-butyl, benzyl, and 4-methylbenzyl nitrate in aqueous ethanol are not accelerated by acids and hence neither the uni- nor the bi-molecular mechanisms is subject to acid catalysis. The carbonyl elimination ($E_{CO}2$) reaction never occurs in such solvolytic decompositions, because the solvent molecules are too weakly basic to effect the removal of the α-hydrogen.

By using benzyl nitrate [with which olefin elimination (E) is structurally impossible] it is shown that continuous decrease in the nucleophilic power of the reagent towards carbon results in the familiar decrease in the velocity of the S_N2 reaction until, finally, a change over to the S_N1 mechanism occurs. Such nucleophilic power does not run parallel with the basic strength of the reagent, *i.e.*, its proton affinity, indicated by the speeds of the concurrent $E_{CO}2$ reaction, which can only proceed by a bimolecular mechanism. Hence the velocity decrease in this reaction caused by continuous decrease in the basic strength of the reagent is now followed by its complete suppression. It is shown that earlier observations regarding the supposed suppression of carbonyl "oxidation" products by addition of "reducing" agents such as quinol (H_2Q) or thiophenol are actually due to an ion-exchange of the type $H_2Q + OEt^- \rightleftharpoons HQ^- + HOEt$, which replaces the strongly basic OEt^- by a much more weakly basic ion (HQ^- or PhS^-), unable to effect the elimination of the α-hydrogen required for the $E_{CO}2$ reaction, whilst the great nucleophilic power of the PhS^- ion towards carbon enormously increases the velocity of the S_N2 reaction.

IN Parts I and II (*J.*, 1952, 1193, 1208) the theory that the complex products formed by hydrolytic decomposition of organic nitrates are consistently and adequately explained on the basis of three simultaneous reactions, *viz.*, (i) nucleophilic substitution at $C_\alpha(S_N)$,† (ii) olefin elimination at H_β (E), and (iii) carbonyl elimination at H_α (E_{CO}), was established experimentally for hydrolyses in neutral and alkaline media. In this communication attention is focused on two other aspects of the problem, *viz.*, (1) hydrolyses in acid media and (2) the effects of change in the attacking nucleophilic reagent on the substitution and the elimination reactions. Both are related to certain observations in the literature which need re-examination in the light of the mechanism now proposed for the production of nitrite and "oxidised" (carbonyl) products.

(A) *Hydrolyses in acid media.*

Theoretically all three reactions, S_N, E, and E_{CO}, might be subject to acid catalysis. By co-ordination of a proton the nitric ester could afford its conjugate acid which could then undergo substitution and elimination reactions by either uni- or bi-molecular mechanisms in a manner similar to that already established for carboxylic esters (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686), *e.g.*, for the unimolecular mechanisms:

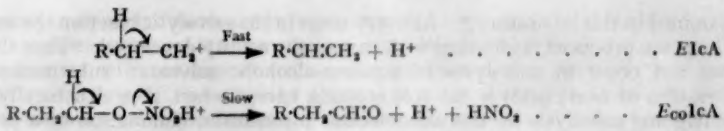
$$R{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}NO_2 + H_3OR^+ \rightleftharpoons R{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}NO_2H^+ + HOR \quad (R=H \text{ or Et}) \quad . \quad (1)$$

$$R{\cdot}CH_2{\cdot}CH_2{\overset{\curvearrowright}{O}}{-}NO_2H^+ \xrightarrow{\text{Slow}} R{\cdot}CH_2{\cdot}CH_2^+ + HNO_2$$

$$R{\cdot}CH_2{\cdot}CH_2^+ + Y \xrightarrow{\text{Fast}} R{\cdot}CH_2{\cdot}CH_2{\cdot}Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad S_N1cA$$

* Part III, *J.*, 1954, 3225.

† *Note added*, 19.1.55: In primary *alkyl* nitrates some attack at the nitrogen atom is now known to occur (Anbar, Dostrovsky, Samuel, and Yoffe, *J.*, 1954, 3603).



Formulation of the corresponding bimolecular mechanisms is obvious. For nitrates which exhibit borderline S_N2–S_N1 characteristics such acid catalysis, by greatly increasing the electron-attracting power of the separating group, might, if it occurs, cause a change over from bi- to the uni-molecular mechanism. The formation of carbonyl compounds and nitrite under acid conditions has been recorded by R. C. Farmer (*J.*, 1920, **117**, 810) and by Lucas and Hammett (*J. Amer. Chem. Soc.*, 1942, **64**, 1928), whilst autocatalysis was reported by Silberrad and R. C. Farmer in the hydrolysis of nitrocellulose (*J.*, 1906, **69**, 1759) and by Biron in the case of ethyl nitrate in aqueous solution (*Chem. Zentr.*, 1901, **1**, 365).

We have examined the effect of both liberated and initially added acid on the rates of hydrolysis of various organic nitrates typical of different mechanistic ranges, *viz.*, ethyl (S_N2), *iso*propyl, benzyl, and 4-methylbenzyl (S_N2–S_N1 borderline), and *tert.*-butyl (S_N1), in aqueous ethanol. In such solvents reaction of liberated nitric acid with the solvent introduces complications when the alcohol content is high and the rate of solvolysis of the nitrate is very slow. A blank experiment with 0·01M-nitric acid in 90-vol. % aqueous ethanol at 60° showed negligible reduction in acidity up to 400 hours, but thereafter acidity was removed at an increasing rate. Initial attack appears to be pure

TABLE 1. *Acid solvolysis of* R·O·NO_2 *in* x% *aqueous ethanol.*

R	Solvent, *x*%	Temp.	Initial [HNO_3]	Initial [HCl]	Final [HNO_3]	10^5k_1, sec.$^{-1}$
Et	45	60°	—	—	0·0171	0·0158 ± 0·0001
Pr^i	60	60·2	—	—	0·0225	{ 0·0497 ± 0·0009 * / 0·0487 ± 0·0005 †
,,	,,	,,	($CaCO_3$ added)	—	—	0·0492
Bu^t	90	60·2	0·0100	—	0·0340	3·95 ± 0·04
,,	,,	,,	0·0592	—	0·0798	4·11 ± 0·03
,,	90, +0·5M-NMe_4NO_3	,,	0·0120	—	0·0480	3·90 ± 0·01
CH_2Ph	45	,,	—	—	0·0200$_4$	4·28 ± 0·08
,,	,,	,,	0·0561	—	0·0770	4·30 ± 0·10
,,	45, +0·5M-KNO_3	,,	—	—	0·0208	4·26 ± 0·02
,,	60	,,	—	—	0·0418	1·71 ± 0·01
,,	,,	,,	—	0·1035	0·0492	1·83 ± 0·02
,,	100	,,	—	—	0·0123	1·19 ± 0·01
p-Me·C_6H_4·CH_2	90	60·5	—	—	0·0415	1·95 ± 0·01
,,	,,	,,	—	0·1019	0·0396	1·94 ± 0·03

* H_3O^+ determination. † NO_3^- determination.

esterification (no nitrite produced), followed by increasing attack involving oxidation of the solvent with production of nitrite. Addition of 0·036M-*iso*propyl alcohol had no effect on the acid removal, indicating that the solvolysis reaction (of *iso*propyl nitrate) is not appreciably reversible under the conditions used. With solvents of lower alcohol content no attack of nitric acid on the solvent occurs for long periods; *e.g.*, in 60% aqueous-ethanolic solution initially containing 0·02M-nitric acid, 0·015M-*iso*propyl alcohol at 60° showed no appreciable drop in acidity until ~1000 hours. Hence, in every case, blank experiments have enabled conditions to be chosen so that accurate determination of the rate of solvolysis was achieved before any appreciable attack on the solvent by nitric acid occurred. With the more rapid reactions with *tert.*-butyl and benzyl nitrate this was possible even in 90% and 100% alcohol. The results obtained with all the nitrates investigated are given in Table 1, where the values of k_1 are the mean of at least ten concordant observations. All velocity coefficients in this paper are in terms of moles, litres, and seconds.

Neither nitrite nor carbonyl formation has been detected in the ***solvolytic*** reaction in aqueous alcohol of any of the large number of mononitrate esters which have now been

examined in this laboratory.* At every stage in the solvolytic reaction the concentration of nitrate ion produced is identical with that of the acidity developed. Thus the E_{CO} reaction does not occur in solvolyses in aqueous-alcoholic solvents; substitution at C_α (with liberation of nitric acid) is the sole reaction except when, in a structurally suitable ester undergoing solvolysis by the unimolecular mechanism, elimination of a proton from the carbonium ion first produced gives rise to concomitant olefin formation ($E1$). All the evidence, as Lucas and Hammett themselves recognized (*loc. cit.*), indicates that the production of benzaldehyde which they observed in the solvolysis of benzyl nitrate in 60% aqueous dioxan arises from a distinct oxidation reaction which is most probably a peroxide-catalysed, free-radical reaction involving homolytic and not heterolytic fission. We have used their observation as a control experiment for the negative results obtained in aqueous-alcoholic solution. Parallel experiments, with the same sample of benzyl nitrate, were set up, one in aged 60% aqueous dioxan and the other in 60% aqueous alcohol. Nitrite and benzaldehyde production were readily detected in the former but were completely absent in the latter.

As the results in Table 1 show, no evidence of acid catalysis was obtained. In any one run the first-order velocity coefficient remained constant throughout, showing no upward drift as the medium became increasingly acid, and its value was unchanged when neutrality was maintained throughout by the presence of calcium carbonate. Initial addition of nitric or hydrochloric acid in concentrations up to 0·1N caused no significant increase in the rate constant, and the absence of appreciable salt effects was indicated by the observation that addition of similar concentrations of potassium or tetramethylammonium nitrate also caused no detectable change in rate.

We are thus unable to confirm (at least for the solvolysis of simple *mono*-nitrate esters in aqueous-alcohol) earlier observations either of acid catalysis or of the production of nitrite and " oxidised " products in such solvolytic reactions.

This absence of acid catalysis is in harmony with the general observation (Olivier and Berger, *Rec. Trav. chim.*, 1922, **41**, 637) that esters of strong acids, unlike carboxylic esters, are not subject to acid-accelerated hydrolyses in aqueous media. This means that although the equilibrium

$$R'\cdot CO\cdot OR + H_3O^+ \rightleftharpoons R'\cdot CO\cdot OHR^+ + H_2O$$

affords a sufficiently high concentration of the conjugate acid $R'\cdot CO\cdot OHR^+$ to cause a rapid, acid-accelerated fission, the equilibrium (1) (p. 608) must be displaced essentially to the left. The difference between the two types $RO\cdot COR'$ and $RO\cdot NO_2$ probably arises from the much greater loss of resonance stabilisation which would result from proton-addition to the nitric ester. The loss of resonance energy consequent on the formation of the conjugate acid, $(\bar{O}\text{–}\overset{+}{N}\text{=}O \longleftrightarrow O\text{=}\overset{+}{N}\text{–}\bar{O}) \longrightarrow HO\text{–}\overset{+}{N}\text{=}O$, would be greater than in $(>C\text{=}O \longleftrightarrow >\overset{+}{C}\text{–}\bar{O}) \longrightarrow >\overset{+}{C}\text{–}OH$, and this difference in basicities of nitro- and carbonyl compounds is confirmed by the fact that simple ketones behave as fully ionised bases in 100% sulphuric acid whereas mononitro-compounds are weak bases even in this medium, nitromethane, for example, being only 20% ionised (Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 58, 60). Proton addition to the alkyl-oxygen atom should cause considerable loss of resonance stabilisation in both systems, $RO\cdot\underset{|}{C}\text{=}O \longleftrightarrow RO\text{=}\overset{+}{\underset{|}{C}}\text{–}\bar{O}$ and $RO\text{–}\underset{\bar{O}}{\overset{+}{N}}\text{=}O \longleftrightarrow RO\text{=}\underset{\bar{O}}{\overset{+}{N}}\text{–}\bar{O}$ but Cowley and Partington (*J.*, 1933, 312, 1252), from a comparative study of the dipole moments of nitro-compounds $R\cdot NO_2$ and nitric esters $RO\cdot NO_2$ conclude that inductive relay of the $-I$ effect of the nitro-group is effectively damped out in the ester by the interposed, unsaturated oxygen atom. This, then, because of its positive character, would be unlikely to behave as a basic centre for attachment of a proton. That the difference in behaviour of the two ester types $\cdot O\cdot COR$ and

* The trace of nitrite, equivalent to <0·3% of E_{CO} reaction, detected in the solvolysis of 4-nitrobenzyl nitrate in 90% ethanol at 75° (Baker and Heggs, following paper) is the only exception and is of doubtful significance since it may arise from oxidation of the solvent.

·O·NO_2 does arise from such differences in basic strength is confirmed by the knowledge that, in 100% sulphuric acid, proton-transfer can occur not only to carboxylic esters but also to organic nitrates, with consequent acid-accelerated fission; *e.g.*, EtO·NO_2 + $3H_2SO_4$ ⟶ EtO·SO_3H + NO_2^+ + H_3O^+ + $2HSO_4^-$ (Kuhn, *J. Amer. Chem. Soc.*, 1947, **69**, 1974) These products suggest that in such strongly acid media proton addition occurs at the alkoxy-oxygen atom to give an initial fission $EtO(H)NO_2 \longrightarrow EtOH + NO_2^+$. Preliminary examination of the behaviour of other simple alkyl nitrates in 100% sulphuric acid, however, revealed that more complicated reactions often occur. Thus one of us (J. W. B.) with Dr. Easty found that the solvolysis of *iso*propyl nitrate with 100% sulphuric acid gives much nitrous acid, carbonyl derivatives, and pseudo-acidic products of the nitroparaffin type.

The observation that, in contrast with the nitrates, the hydrolysis of organic nitrites is acid-catalysed (Allen, *J.*, 1954, 1968) is also in harmony with these views. The more strongly basic character of the nitrous esters is doubtless to be associated with the smaller loss in resonance energy which would result from the conversion of the neutral ester RO–N=O ⟷ $R\overset{+}{O}{=}N{-}\overset{-}{O}$ into its conjugate acid.

(B) *Changes in the nucleophilic reagent.*

Since the two elimination reactions, E and E_{CO}, have specific structural requirements, it is possible to exclude one or other and so make a direct study of the relative effects of changing the nucleophilic reagent on the substitution and on one particular elimination reaction. By using benzyl nitrate, olefin formation is excluded, and we have thus studied the comparative effects of decreasing nucleophilic power upon the S_N reaction, in which the attack is at C_α (cf. p. 613), and on the E_{CO} reaction, in which it is at H_α.

The complete absence of the E_{CO} reaction in solvolytic reactions in aqueous alcohol with all the organic nitrates we have investigated is in harmony with the view (Part III, *loc. cit.*) that this reaction occurs only by the bimolecular mechanism, and that neither water nor alcohol molecules are sufficiently basic to effect the removal of the α-hydrogen atom. This interpretation is confirmed by the observation that when the more strongly basic solvent triethylamine is used the production of both nitrite and benzaldehyde is readily demonstrated.

In a good ionising solvent but with a reagent of high nucleophilic activity both the S_N and E_{CO} reactions may proceed by a bimolecular mechanism. Gradual reduction in the nucleophilic power of the reagent will first cause a decrease in the velocity of both reactions. Ultimately, when the reagent is too weakly necleophilic to take part in a S_N2 mechanism, there may be a change over to the unimolecular S_N1 mechanism and the rate will now be constant and independent of the reagent (cf. Gleave, Hughes, and Ingold, *J.*, 1935, 238, Fig. 2). No such alternative is, however, available to the $E_{CO}2$ reaction and hence, when the reagent is too weakly basic to assist in the removal of the α-hydrogen, the E_{CO} reaction will be completely suppressed. Such changes are illustrated by the following results of the action of various nucleophilic reagents, Y, on benzyl nitrate in 45% aqueous alcohol at 60°.

	(*a*)				(*b*)		
Y =	PhO^-	OH^-	p-NO_2·C_6H_4·O^-	$CO_3^=$	$H{\cdot}CO_3^-$	Cl^-	EtOH
10^5k (S_N2)	220	50	(30) *	(14)	—	—	—
10^5k (S_N1)	—	—	—	—	4·30	4·30	4·30
10^5k ($E_{CO}2$)	(9)	106	(~0·2)	(7)	⟵ no reaction ⟶		

* Downward drift 40 ⟶ 20 observed.

The two *groups* of reagents (*a*) of higher nucleophilic power and (*b*) of very weak nucleophilic character show the deductions made above to be verified. Assignment of the actual order of decreasing nucleophilic power within these groups is much more difficult. Various attempts to assign numerical values to nucleophilic power (*e.g.*, Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141; Edwards, *ibid.*, 1954, **76**, 1540) make it

clear that, contrary to the earlier simple assumption, nucleophilic power does not run parallel with proton-acceptor power, *i.e.*, with basicity, and, moreover, varies with the substrate. It is thus not possible to say just where, in a series of reagents of varying nucleophilic power, is the position of the solvent, and this makes it impossible to say with certainty whether, in group (*b*), an actual change over to the unimolecular mechanism has occurred. The same results would be obtained if the other reagents in this group, *viz.*, HCO_3^- and Cl^-, were much more weakly nucleophilic than the solvent molecules. This ambiguity seems to be present in any application of this test for the unimolecular mechanism unless (as, at present, seems difficult) the reagents can be placed in a *correct* order of decreasing nucleophilic power in which the solvent is the weakest. The complications which arise from proton transfer between the solvent and the reagent Y have been examined in Part III (*loc. cit.*), where an attempt was made to eliminate such complications in 100% ethanol, but in mixed aqueous-alcoholic solvents, where three interrelated equilibria are involved, this is more difficult. For this reason the actual values of k ($E_{CO}2$) for PhO^- and CO_3^- have little significance since at least some of the elimination will be due to OH^- and OEt^- ions. The lyate-ion effect (Benfey, Hughes, and Ingold, *J.*, 1952, 2488) with OH^- in a highly aqueous solvent greatly decreases the apparent nucleophilic power of this anion towards carbon, giving the order $PhO^- > OH^-$, for the S_N2 reaction, but leaves its ability to attack hydrogen unimpaired, so that the more usual order $OH^- > OPh^-$ is followed in the $E_{CO}2$ reaction. The reaction course with only a slight excess of sodium carbonate as the reagent is instructive. Initially, the value of a calculated first-order constant for total reaction falls (indicating the superimposition of some second-order reaction) and the concentration of nitrite ion produced increases,

TABLE 2. *Values of k (S_N2) and k ($E_{CO}2$) in l. mole^{-1} sec.$^{-1}$ for the reaction of various nucleophilic reagents* Y *on* $CH_2Ph{\cdot}O{\cdot}NO_2$ *in* 100% EtOH *at* 60°.

Y	$pK_a^{25°}$ † in water	10^5k (S_N2)	10^5k ($E_{CO}2$)	$100k$ ($E_{CO}2$)/[k (S_N2) + k ($E_{CO}2$)]
PhS^-	—	21,000 ‡	—	0
EtO^-	—	100	1345	93
p-MeO·C_6H_4·O^-	10·16	110	5·63	4·9
PhO^-	9·95	60	3·8	5·9
m-NO_2·C_6H_4·O^-	8·35	13·7	0·217	1·6
p-NO_2·C_6H_4·O^-	7·14	5·0	0·085	1·7
C_5H_5N	5·13	4·0	(Nil)	0
EtOH	—	0·007 *	(Nil)	0

* k (S_N2) = k_1[EtOH] = {0·119 ÷ 17·2} × 10^{-5}.
† Judson and Kilpatrick, *J. Amer. Chem. Soc.*, 1949, **71**, 3110.
‡ Extrapolated from values at 20° and 30°.

both regularly, until, at ~50% reaction, the liberated nitric acid has converted all the original CO_3^- ion into the much more weakly nucleophilic HCO_3^- ion. For the remainder of the run the nitrite concentration then remains unchanged, showing that the E_{CO} reaction has how been suppressed, whilst the value of the first-order velocity coefficient becomes identical with that for the solvolysis reaction (cf. p. 615). With a higher initial [Na_2CO_3], corresponding to approximately a four-fold excess, complete conversion into bicarbonate cannot occur and, in this case, nitrite production continues throughout the whole run but the values of k ($E_{CO}2$) and, to a smaller extent, of k (S_N2), fall continuously as the reaction progresses. The conversion $CO_3^- + H^+ \longrightarrow HCO_3^-$ begins as soon as any nitric acid has been liberated, and hence the recorded values of k ($E_{CO}2$) and k (S_N2) are those obtained by extrapolation to zero reaction in this experiment.

In a solvent of low ionising power, such as 100% alcohol, transition to the unimolecular mechanism is less likely. In such a case decrease in the nucleophilic power of the reagent should cause a continuous decrease in the velocity of the S_N2 reaction. Since nucleophilic activity towards hydrogen diminishes much more rapidly than that towards carbon, the accompanying $E_{CO}2$ reaction should exhibit a more rapid fall in velocity until, when the reagent is devoid of nucleophilic activity towards hydrogen, it is completely suppressed. These conclusions are verified by the results in Table 2, where the values for both k (S_N2) and k ($E_{CO}2$) for the aryloxides are the true values (determined by suppression of proton exchange) obtained in Part III (*loc. cit.*). A strong lyate-ion effect, now with

ethoxide in dry ethyl alcohol, is apparent in the substitution reaction, this reagent being less effective than the *p*-methoxyphenoxide ion. The satisfactory straight-line Brönsted plots between pK_a with either k ($E_{CO}2$) or k (S_N2) were noted in Part III; the value for EtO^- falls satisfactorily on the k ($E_{CO}2$)–pK_a curve, but is some 80 times too low to fit on the k (S_N2) plot. The enormously greater nucleophilic activity towards carbon of the more weakly basic thiophenoxide ion compared with that of phenoxide is reflected in both the energy and entropy factors in the Arrhenius equation:

	E, kcal. mole^{-1}	$\log_{10} A$		E, kcal. mole^{-1}	$\log_{10} A$
PhO^-	19·3	9·5	PhS^-	17·5	10·7

Such high nucleophilic activity of the thiophenoxide ion towards carbon (a first-period element) is well known but not completely understood, and it is perhaps significant that it does not seem to be observed when the nucleophilic attack is at a second-period element, since Dostrovsky and Halmann (*J.*, 1953, 508) found that, for attack on phosphorus, the order of activity in ethanol solution was $PhO^- > EtOH > PhS^-$, the thiophenoxide ion causing no increase in the observed rate of solvolysis. The specific implications of the high nucleophilic activity of thiophenoxide towards carbon, coupled with its lack of reaction with hydrogen, are discussed below.

To complete our verification of expected velocity relationships we have examined the effect of various reagents on the decomposition of *tert.*-butyl nitrate in 90% aqueous alcohol. Here carbonyl elimination is structurally excluded and the unimolecular mechanism ($S_N1 + E1$) has previously been established. The results are in Table 3.

TABLE 3. *Hydrolytic decomposition of* $Bu^t{\cdot}O{\cdot}NO_2$ *in* 90% *aqueous* EtOH *at* 20° *in the presence of* 0·05M-Y.

Y	OR^- *	N_3^-	Cl^-	NO_3^-	EtOH
$10^5 k_1$	4·51	4·60	4·40	3·90	3·99

* R = Et, H due to $HO^- + EtOH \rightleftharpoons EtO^- + H_2O$.

Evidently the total reaction ($S_N + E$) is following the unimolecular mechanism and is independent of the nature and concentration of any added reagent. The small increase in velocity observed in the presence of 0·05M-OR^-, -N_3^-, and -Cl^- ions is almost certainly due to an ionic-strength salt effect which, in the case of the same concentration of NO_3^-, is nullified by a common-ion, mass-law effect on the reversible ionisation $Bu^tNO_3 \rightleftharpoons Bu^{t+} + NO_3^-$. The new value for k_1 ($S_N + E$) is ~8% higher than that of Baker and Easty (*J.*, 1951, 1201), owing probably to a slight difference in solvent composition and improvements in technique which have been developed. The velocity increase caused by addition of ~0·05M-hydroxide ion is, however, smaller than that previously observed (*idem, ibid.*) when a larger $[OH^-]$ was added.

The observed suppression of the E_{CO} reaction with weakly nucleophilic reagents provides a satisfactory explanation of the recorded effects of "reducing" agents in preventing the formation of "oxidation" products in the hydrolytic decomposition of organic nitrates. Thus the suppression of "oxidised" products in the alkaline hydrolysis of the polynitrates of glycerol and cellulose by addition of thiophenol (Klason and Carlson, *Ber.*, 1907, **40**, 4183) we regard as due to the replacement of the strongly basic hydroxide ion by the thiophenoxide ion, $HO^- + PhSH \rightleftharpoons PhS^- + H_2O$, which, as our results show, is unable to effect the carbonyl-elimination reaction. Their reported formation of free glycerol and cellulose (rather than their phenylthio-derivatives) is less easily explained, especially in view of Carlson's observation (*ibid.*, p. 4191), which we have confirmed, that a quantitative yield (we obtained 96%) of benzyl phenyl sulphide can be isolated from the action of sodium thiophenoxide on benzyl nitrate. In the kinetic examination, the disappearance of PhS^- is accompanied by the equivalent formation of NO_3^- showing that the reaction is entirely a nucleophilic substitution at carbon. Recently, however, Morrow, Cristol, and van Dolah (*J. Amer. Chem. Soc.*, 1953, **75**, 4259) obtained only *n*-butyl alcohol from the reaction of *n*-butyl nitrate with sodium hydrogen sulphide in aqueous alcohol, no trace of *n*-butanethiol being detected. They formulated the reaction as the attack of the polysulphide ion on either oxygen or nitrogen, but in our

investigations we have found no evidence that, in the substitution reaction, nucleophilic attack ever occurs anywhere other than at carbon (but cf. footnote, p. 608).

Ion exchange doubtless explains the suppression of benzaldehyde formation by added quinol (H_2Q) observed by Lucas and Hammett (*loc. cit.*) in the hydrolytic decomposition of benzyl nitrate in 60% aqueous dioxan. In this case, however, the problem is not quite so straightforward. We have already given reasons why we believe that the *whole* of the observed benzaldehyde formation in the *solvolysis* of benzyl nitrate in 60% aqueous dioxan arises from a peroxide-catalysed, chain reaction, and its complete suppression by the antioxidant, quinol, observed by Lucas and Hammett, would thus be expected. These authors, however, also record the complete suppression of benzaldehyde formation in the *alkaline* hydrolysis of benzyl nitrate by addition of quinol in concentration $< [OH^-]/2$. In alkaline media there will certainly be some $E_{CO}2$ reaction, and our interpretation of the effect of added quinol is that, because of the equilibrium $OH^- + H_2Q \rightleftharpoons HQ^- + H_2O$, the strongly basic hydroxyl ion is replaced by the much more weakly basic *p*-hydroxyphenoxide ion which is unable to effect carbonyl elimination. For complete suppression of the $E_{CO}2$ reaction the concentration of added quinol would need to be sufficiently high to displace the equilibrium completely over to the right so that $[OH^-]$ becomes effectively zero. In agreement with this view, our results (Table 4) show that, in 60% alcohol, the reduction in the proportion of nitrite (benzaldehyde) formation is greater the larger is the concentration of added quinol, but it is certainly not completely suppressed until $[H_2Q] \geqslant [OH^-]$. The uncertainty whether, with sufficiently high $[H_2Q]$ complete suppression of benzaldehyde formation occurs, arises from our observation than high concentrations of quinol interfere with the determination of nitrite, whilst the unavoidable presence of some benzoquinone gives unreliably high values for the determination of benzaldehyde as its 2 : 4-dinitrophenylhydrazone.

TABLE 4. *Effect of added quinol* (H_2Q) *on the hydrolysis of* 0·0320M-$CH_2Ph{\cdot}O{\cdot}NO_2$ *with* 0·0371N-KOH *in* 60% *aqueous ethanol.*

	$[NO_3^-]$ or [Ph·CHO]			
Time (min.)	No H_2Q	0·001M-H_2Q	0·02M-H_2Q	0·06M-H_2Q
0	0·00084	0·000785	0·00059	—
45	0·00577	0·00546	0·00273	—
125	0·01030	0·00942	0·00702	0·000904
300	0·01403	0·01341	—	—
	—— Progressive reduction in E_{CO} reaction ——→			

Lucas and Hammett observed that the suppression of benzaldehyde formation in alkaline media by quinol was accompanied by an increase in the overall rate of hydrolysis of benzyl nitrate. In the light of our values of k (S_N2) for the *p*-methoxyphenoxide ion compared with ethoxide in 100% alcohol (Table 2), and for phenoxide and hydroxide in 45% alcohol (p. 611), their observed increase might well be accounted for by the increased velocity of the substitution reaction by the HQ^- ion. The superimposition of both heterolytic and homolytic reactions of benzyl nitrate under the experimental conditions used by Lucas and Hammett, however, makes the interpretation of their results complicated. In aqueous-alcohol solvents, in which only heterolytic fissions occur, we have found that the change in the nucleophilic power of the attacking reagent as it affects the S_N2 and $E_{CO}2$ reactions provides an adequate explanation of the effects of added thiophenol or quinol and that our new experimental results amply confirm the view regarding the mechanism of the hydrolytic decomposition of organic nitrates put forward in Part I of this series.

EXPERIMENTAL

Preparation of Solvents and Materials.—Details relating to the solvent and the phenolic reagents used were given in Part III (*loc. cit.*); x% aqueous-ethanolic solutions containing free nitric or hydrochloric acid were prepared by adding $(100 - x)$ volumes of aqueous solutions containing the required amount of acid to x volumes of dry ethanol. Other reagent solutions were prepared by direct dissolution of the required weight of the pure reagent in the x% ethanol, with exclusion of moisture and carbon dioxide throughout. Ethyl, *iso*propyl, and *tert.*-butyl

nitrate were prepared and purified as described in Part I (*loc. cit.*), and benzyl nitrate as in Part III (*loc. cit.*).

Tetramethylammonium nitrate was prepared from the iodide and "AnalaR" aqueous silver nitrate and was crystallised from aqueous alcohol. Purity by gravimetric determination of NO_3^- = 99·7%.

Velocity Determinations.—The techniques were those described in Part III. Appropriate titrimetric techniques and indicators were chosen for each reagent. The following are not recorded in Part III.

Thiophenoxide.—The minute amount of nitrite produced with this reagent was too small to interfere, and permitted determination of thiophenoxide by arresting the reaction by delivery into a known excess of alcoholic hydrochloric acid and titration of the excess acid with 0·02N-sodium hydroxide, bromophenol-blue being the indicator.

Carbonate and Bicarbonate.—Carbonate and bicarbonate were determined in the aqueous solution, after ether-extraction, by direct titration with 0·01N-sulphuric acid (methyl-red indicator) and boiling to expel carbon dioxide.

Pyridine.—Since this reagent is retained by ether its determination must be effected in the presence of unchanged benzyl nitrate. This prevented its titration with acid and screened methyl-yellow because the indicator was removed from the aqueous phase by the ester. The reaction was followed by gravimetric determination of nitrate on the aqueous extract (Baker and Easty, *loc. cit.*).

Reactions with azide and chloride ions were followed by direct titration with 0·01N-sodium hydroxide, checked, in the case of the former reagent, by gravimetric determination of the nitrate ion produced.

The separate velocity coefficients were calculated by the methods described in Part III. The following are typical runs.

(1) *Acid hydrolysis.* Initial [$Ph{\cdot}CH_2{\cdot}O{\cdot}NO_2$] = 0·0280M; [$HNO_3$] = 0·0561M in 45% ethanol at 60·2°.

Time (min.)	0	45	130	165	225	285	315	345	375	476	525
10^3[HNO_3], mole $l.^{-1}$	57·5	60·4	65·2	66·8	69·2	71·3	72·4	73·1	73·9	76·3	77·0
10^5k_1, sec.$^{-1}$	—	4·24	4·39	4·34	4·27	4·29	4·34	4·27	4·26	4·28	4·18

(2) *Action of sodium carbonate in 45% ethanol (mole/l.) on benzyl nitrate (0·02856M) at 60°.*

Time (min.)	0	30	70	110	151	190	230
10^3[Na_2CO_3] *	3·835	3·57	3·275	3·03	2·82	2·64	2·48
10^5k_1	—	5·43	5·18	5·03	4·82	4·74	4·63
10^3[NO_3^-]	0·054	0·229	0·451	0·551	0·600	0·630	0·643

Time (min.)	270	320	380	440	514	580	630
10^3[Na_2CO_3] *	2·35	2·20	1·995	1·85	1·71	1·64	1·52
10^5k_1	4·53	4·44	4·53	4·49	4·41	4·21	4·39
10^3[NO_3^-]	0·643	0·643	0·643	0·643	0·630	0·630	0·630

* Initially Na_2CO_3, subsequently $NaHCO_3$.

(3) *Action of* NaOEt *on* $Ph{\cdot}CH_2{\cdot}O{\cdot}NO_2$ *in* 100% EtOH *at* 60° (*corrected for reaction before zero time*). Initially [NaOEt] = 0·03664M, [$Ph{\cdot}CH_2{\cdot}O{\cdot}NO_2$] = 0·03007M.

Time (min.)	0	20	40	50	60	70	80	90	105	130	150
10^3[NaOEt]	3·367	2·331	1·833	1·627	1·527	1·428	1·347	1·259	1·196	1·078	0·991
10^3k_2	—	1·45	1·44	1·52	1·46	1·45	1·44	1·47	1·40	1·41	1·48
10^3[NO_3^-]	—	0·999	1·431	1·581	1·717	1·801	1·1884	1·953	2·028	2·157	2·195
E_{CO}, %	—	96·4	93·3	90·1	93·3	93·8	93·3	92·6	93·4	93·2	92·7

Equivalence of [NO_3^-] + [NO_3^-] *and* [*Acid*] = [OEt^-] *removed.*

Time (min.)	50	70	90	120	150	160	195
(*a*) 10^3[NO_3^-]	1·754	1·974	2·126	2·271	2·368	2·386	2·440
(*b*) 10^3[NO_3^-]	0·250	0·278	0·290	0·305	0·333	0·326	0·348
10^3 [(*a*) + (*b*)]	2·004	2·252	2·416	2·576	2·701	2·712	2·788
10^3 [Acid]	2·038	2·237	2·406	2·550	2·674	2·711	2·763

Equivalence of [NO_3^-] *and* [Ph·CHO].

Time (min.)	20	160	1 week
10^3[Ph·CHO]	1·161	2·391	2·610
10^3[NO_3^-]	1·172	2·386	2·619

Effect of concentration changes.

[NaOEt]	[$Ph{\cdot}CH_2{\cdot}O{\cdot}NO_2$]	10^3k_2 (total)	10^3k ($E_{CO}2$)	10^3k (S_N2)
0·034	0·027	1·45	1·35	0·10
0·060	0·04	1·47	1·37	0·10
0·100	0·04	1·48	1·34	0·14

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Hydrolytic Decomposition of Esters of Nitric Acid. Part V. The Effects of Structural Changes in Aralphyl Nitrates on the S_N and E_{CO} Reactions.*

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Solvolytic and alkaline hydrolytic decomposition of *o*-, *m*-, and *p*-nitrobenzyl, *p*-bromobenzyl, benzyl, *p*-methylbenzyl, *p*-methoxybenzyl, diphenylmethyl, and 1- and 2-phenylethyl nitrates have been studied kinetically in aqueous-ethanolic solvents at several temperatures by methods which make possible the separate evaluation of k_1 (solvoiysis), k (S_N2), k ($E_{CO}2$), and, where applicable, k ($E2$). On the basis of these results an analysis has been made of the effects of structural and environmental changes on each separate reaction in terms of the Arrhenius parameters.

In the substitution reaction (by solvent molecules or hydroxide ion) these nitrates closely resemble the corresponding chlorides. In both 90% and 60% aqueous ethanol the first five nitrates follow the S_N2 mechanism, whilst a change to the unimolecular mechanism is observed with *p*-methoxybenzyl, diphenylmethyl, and 1-phenylethyl nitrates. *p*-Methylbenzyl nitrate is a borderline case since it follows the S_N2 mechanism in 90% alcohol but is predominantly S_N1 in the more ionising 60% alcohol.

The specifically bimolecular $E_{CO}2$ reaction is particularly susceptible to structural changes and is favoured (1) by conjugation of the 1-phenyl substituent with the forming carbonyl bond and (2) by strongly electron-attracting substituents in this benzene ring which greatly facilitate the separation of a proton from C_α by increasing the strength of the nitric ester as a pseudo-acid. Introduction of a second α-substituent (alkyl or phenyl), although it may increase the speed of the $E_{CO}2$ reaction, actually greatly reduces its relative proportion because of the concomitant very large increase in the velocity of unimolecular solvolysis, which thus becomes the main reaction.

A sensitive and accurate amperometric titration method for determination of styrene has been applied to the preliminary examination of the olefin-elimination reactions in 1- and 2-phenylethyl nitrates.

EXAMINATION of the effect of structural changes in the nitric ester itself on the relative velocities and importance of the nucleophilic substitution (S_N) and carbonyl-elimination (E_{CO}) reactions has so far been restricted to the alkaline hydrolyses of simple alkyl nitrates (Parts I and II, Baker and Easty, *J.*, 1952, 1193, 1208), in which carbonyl elimination never amounted to >10% of the total reaction. It is obviously desirable to examine nitrates in which this reaction path constitutes a larger proportion of the total reaction. In Part IV (*loc. cit.*) it was shown that hydrolytic fission of benzyl nitrate with hydroxide or ethoxide ions gives rise to a high proportion of nitrite and benzaldehyde formation. Nuclear substitution in this ester (in *m*- and *p*-positions) permits a study of the polar effects of such substituents on the relative velocities and importance of the S_N and E_{CO} reactions without complicating steric effects, whilst α-alkyl substitution introduces the third path, olefin elimination, for inclusion in the study. We have prepared a number of nitrates of the general type $X{\cdot}C_6H_4{\cdot}CHR{\cdot}NO_3$ and have determined their rates of solvolysis and of hydrolytic fission with hydroxide or ethoxide ions in various aqueous-ethanolic solvents at different temperatures, by methods which have permitted evaluation of the separate rate coefficients for solvolysis (k_1), for bimolecular substitution [k (S_N2)], and for bimolecular carbonyl elimination [k ($E_{CO}2$)], together with the corresponding values of the Arrhenius equation parameters. We repeatedly confirmed (see p. 629 and Part IV) that, throughout the whole reaction, $[H_3O^+]$ produced or $[OR^-]$ removed is identical with $[NO_3^-]$ produced when substitution is the sole reaction, and with $[NO_3^-] + [NO_2^-]$ when the carbonyl elimination

* Part IV, preceding paper.

reaction is also present, and that $[NO_3^-] = [R{\cdot}CHO]$. Subsequently, therefore, reactions were followed by the more rapid acid–alkali titrimetric methods and the rapid and accurate colorimetric determination of nitrite.

The incidence of a fairly rapid solvolysis reaction often made separate evaluation of k (S_N2) and k ($E_{CO}2$) a tedious business: four different methods were used and are described in the experimental section (p. 628). The most accurate values are those (k_1) for solvolysis, for which the probable error is $\pm 2\%$ and about ± 300 cal. in the values of the Arrhenius activation energies. The probable errors for k ($E_{CO}2$) are $\pm 3\%$, but for k (S_N2) they are often quite large (see Table 4). It will be convenient to discuss the effects of structural variation in the nitrate on the solvolysis and the S_N2 and $E_{CO}2$ reactions in turn, on the basis of these separated rate constants. Only a preliminary investigation of olefin elimination ($E2$) in 1- and 2-phenylethyl nitrates is included.

(1) *Solvolysis*

The corrected values of k_1 (sec.$^{-1}$), each of which is obtained from at least ten separate evaluations, for solvolyses in aqueous-ethanolic solutions are given in Table 1.

The results are arranged in order of increasing electron-release by the group R, and comparison of values in either solvent at a specific temperature reveals that this is also the order of increasing velocity of solvolysis. Heterolysis of the C–O·NO_2 bond thus seems to be the more important factor. This is confirmed by the 100-fold increase in velocity caused by the introduction of an α-phenyl substituent into methyl nitrate ($10^5k_1^{60°}$ in 60% ethanol = 0·0196; Baker and Easty, *loc. cit.*) which permits the facilitating, conjugative polarisation $\left(\bigcirc\!\!=\!CH_2\right)^+NO_3^-$, whereas the introduction of a 2-phenyl substituent into ethyl nitrate ($10^5k_1^{60}$ in 60% ethanol = 0·01; *idem, ibid.*) reduces the velocity, such polarisation not now being structurally possible. In the halide series benzyl is on the borderline of S_N1–S_N2 mechanism, and in our results we find evidence that the aralphyl nitrates traverse the whole range from bimolecular to unimolecular solvolysis.

We consider first the effect of structural changes as the criterion of mechanism. The relative values ($CH_2Ph = 1$) of k_1 for the solvolysis of RNO_3 at 20°, are given below:

R =	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*p*-$C_6H_4Br{\cdot}CH_2$ *	CH_2Ph
90% EtOH	0·089	0·12	0·52	1
60% EtOH	0·036	0·058	0·41	1

R =	*p*-$C_6H_4Me{\cdot}CH_2$	CHPhMe	*p*-$MeO{\cdot}C_6H_4{\cdot}CH_2$	$CHPh_2$
90% EtOH	5·91	97·4	12,820	36,950
60% EtOH	13·9	566	—	—

* Estimated from results at 60°.

In 90% aqueous ethanol, from *p*-nitrobenzyl to *p*-methylbenzyl nitrate, where decreasing electron-attraction (or increasing release) causes relatively small increases in velocity, the pattern is the familiar one for the S_N2 mechanism. With 1-phenylethyl, *p*-methoxybenzyl, and diphenylmethyl nitrates the very large velocity increases caused by the further increase in the electron-release of R clearly indicate that the solvolysis of these nitrates is proceeding by the unimolecular mechanism. In the more ionising solvent, 60% ethanol, it is evident that the mechanistic change over has now occurred at the *p*-methylbenzyl ester, and the differences in behaviour of this compound in 90% and 60% ethanol are quite marked.

These mechanistic conclusions are confirmed by the sensitivity of the solvolysis rates towards added hydroxide ion. The test cannot be applied to the nitrobenzyl nitrates because, in the presence of alkali, carbonyl elimination becomes practically the sole reaction (p. 625), but the specific rates (10^5k_1) for solvolysis alone and for the isolated substitution reaction in the presence of 0·04M-hydroxide ion are given in Table 2.

It is evident that alkali has no significant effect on the rate of hydrolysis of those nitrates for which it was concluded above that the S_N1 mechanism is operative. The different behaviour of the *p*-methylbenzyl compound in 60% and 90% ethanol is again evident: in

the former the reaction is mainly of first order, whilst a second-order reaction is predominant in the less ionising solvent.

There is, of course, no clear-cut division between the two extreme mechanisms (Gleave, Hughes, and Ingold, *J.*, 1936, 236) which are differentiated by different degrees of co-operation of solvent molecules in the rate-determining stage. Both mechanisms involve

TABLE 1. *Values of the first-order coefficient* k_1 *(sec.*$^{-1}$*) and Arrhenius parameters for the solvolysis of* RNO_3 *in* x% *aqueous ethanol at various temperatures.*

x	Temp.	10^5k_1	E, kcal./mole	log A
	R = Ph·CH_2·CH_2			
60	75·0°	0·01	—	—
	R = *p*-NO_2·C_6H_4·CH_2			
90	96·2	0·853	23·1	8·6
,,	75·0	0·122		
,,	60·2	0·0281		
,,	45·0	0·0052		
60	96·2	2·70	24·1	9·7
,,	75·0	0·361		
,,	60·2	0·0760		
,,	45·0	0·0136		
	R = *m*-NO_2·C_6H_4·CH_2			
90	95·0	0·950	22·8	8·5
,,	75·0	0·161		
,,	60·2	0·0366		
60	95·0	3·63	23·7	9·3
,,	75·0	0·577		
,,	60·2	0·1267		
,,	45·0	0·0228		
	R = *p*-BrC_6H_4·CH_2			
90	60·2	0·190	—	—
60	60·2	0·813	—	—
	R = Ph·CH_2			
90	60·2	0·341	23·4	9·9
,,	45·0	0·0624		
,,	30·0	0·0101		
60	60·2	1·80	23·6	10·8
,,	45·0	0·334		
,,	30·0	0·0527		
	R = *p*-CH_3·C_6H_4·CH_2			
90	75·0°	8·71	23·2	10·6
,,	60·2	2·00		
,,	45·0	0·367		
	R = *p*-CH_3·C_6H_4·CH_2			
60	60·2	31·6	24·3	12·5
,,	45·0	5·53		
,,	19·85	0·196		
	R = Ph·CHMe			
90	60·2	39·6	24·2	12·5
,,	20·0	0·262		
60	20·0	8·32	24·5	14·2
,,	0·0	0·378		
	R = *p*-MeO·C_6H_4·CH_2			
90	20·0	34·5	—	—
	R = Ph_2CH			
100	30·0	45·0	23·7	13·8
,,	20·0	11·8		
,,	10·0	2·80		
90	20·0	99·4	22·3	13·7
,,	10·0	26·6		
,,	0·0	6·06		

TABLE 2. *Values of specific rates* (10^5k_1 *sec.*$^{-1}$) *for the substitution reaction of* RNO_3 *in* x% *aqueous* EtOH *at* 20° (a) *without alkali and* (b) *with* 0·04M-*alkali.*

R	x = 60 a	x = 60 b	x = 90 a	x = 90 b
Ph_2CH	(11·8	13·2) *	99·4	100
p-MeO·C_6H_4·CH_2	—	—	34·5	34·2
PhCHMe	8·32	8·02	0·262	0·284
C_6H_4Me·CH_2	0·204	0·265	0·0159	0·118
Ph·CH_2	0·0147	0·060	0·00269	0·058
p-C_6H_4Br·CH_2	0·0060	0·088	0·0014	0·13

* In 100% EtOH.

an increase in charge in the transition state and hence the velocity of both should be increased in the more aqueous solvent. Experience suggests (cf. Baker and Easty, *J.*, 1952, 1211) that such increase is more pronounced for the S_N1 mechanism. Relative velocities in different aqueous ethanolic media are given in Table 3, those in 90% ethanol being taken as standard. Data for methyl nitrate (S_N2) and for *tert.*-butyl and diphenylmethyl chlorides (S_N1) are included as reference standards. Comparisons confirm that, of the nitrates given, only the diphenylmethyl and 1-phenylethyl esters are undergoing solvolysis by the S_N1 mechanism, whilst *p*-methylbenzyl nitrate is on the S_N2–S_N1 borderline.

In a plot of log k_1 (as ordinates) of substituted benzyl nitrates against Hammett's σ values (" Physical Organic Chemistry," McGraw-Hill, 1940, p. 190) for the nuclear substituents, the values for *m*- and *p*-nitro-, hydrogen, and *p*-bromo- fall on a straight line but *p*-methyl and, especially, *p*-methoxyl introduce a marked upward curvature. Hammett's use of ionisation constants derived from carboxylic acids as a measure of values automatically excludes polarisability effects and it is evident that the facilitating $+E$ effect of *p*-methyl

TABLE 3. *Relative velocities of solvolysis of* RNO_3 *at* 20° *in* x% *aqueous* EtOH.

x	R = Ph_2CH	PhCHMe	*p*-$C_6H_4Me{\cdot}CH_2$	$PhCH_2$	*p*-$C_6H_4Br{\cdot}CH_2$
100	0·12	—	—	0·36 *	—
90	1·0	1·0	1·0	1·0	1·0
60	—	32	13	5·5	4·2
45	—	—	—	12·5 *	—

x	*m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	CH_3 †	Bu^tCl ‡	Ph_2CHCl ‡
100	—	—	—	0·054	0·11
90	1·0	1·0	1·0	1·0	1·0
60	2·6	2·2	2·7	73·5	—
45	—	—	—	400	—

* Baker and Neale, *loc. cit.* † Baker and Easty, *loc. cit.*
‡ From data collected by Winstein and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 846; 1951, **73**, 2701.

and, particularly that of *p*-methoxyl, will play an important rôle in the solvolysis. Moreover, these effects introduce a change in mechanism which will almost certainly be accompanied by a change in the reaction constant; accordingly, the marked curvature of the Hammett plot confirms conclusions reached on other evidence.

The intelligible picture presented by the solvolysis rates is in marked contrast to the superficial confusion suggested by the Arrhenius activation energies, for which the continuous transition between two distinct mechanisms is largely responsible. Interpretation of the Arrhenius parameters has been discussed in detail by one of us elsewhere (Heggs, Thesis, University of Leeds, 1954) and only a few salient points can be mentioned here. Differences in the E_A values are small and not very much larger than the estimated experimental accuracy ($\pm$0·3 kcal.). In the region of bimolecular solvolysis the polar character of the nuclear substituent will have opposite effects on the ease of breaking of the C–O·NO_2 bond* and the electrostriction of, and bond formation by, the attacking solvent molecule. This dual polar requirement evidently means that such substitution has little overall effect on the value of E_A, the main differences being in the entropy term. The unimolecular solvolysis, however, derives no help from covalent interaction with the solvent molecule and hence if, in a graded series of nitrates with increasing electron-release towards C_α there is, at any point, a rather rapid transition from S_N2 to S_N1, a higher E_A value might well result. In agreement with our earlier deductions, such a definite increase in E_A is observed on passing from *p*-methylbenzyl to 1-phenylethyl nitrate in 90% ethanol and between benzyl and *p*-methylbenzyl nitrates in 60% ethanol. Once in the unimolecular region, further increase in electron supply at the reaction site will decrease the energy required for heterolysis, and the lower E_A values for diphenylmethyl nitrate are understandable. The entropies of activation fit into the same picture. For those nitrates which, as suggested by other evidence, are undergoing essentially a bimolecular solvolysis the values of log A (after allowance for the inclusion of a solvent concentration term) are of the same order of magnitude as those observed in other known bimolecular reactions (*e.g.*, the Menschutkin reaction) of the same charge type. Unimolecular solvolyses frequently have non-exponential terms of the order 10^{13} and it is again significant that such values are observed for those nitrates to which we have assigned the S_N1 mechanism. Benzyl nitrate in 60% and its *p*-methyl derivative in 90% ethanol show distinct transition tendencies. The effect of α-substituents in increasing the entropy of activation in the unimolecular mechanism was ascribed by A. G. Evans and Hamman (*Trans. Faraday Soc.*, 1951, **47**, 25) to a displacement of solvent molecules from the first solvation shell, thereby diminishing

* *Note added*, 19.1.55—Evidence was given by Baker and Neale (*J.*, 1954, 3225; Part IV, *loc. cit.*) that with benzyl nitrate nucleophilic substitution occurs solely at C_α.

the solvation of the cation. The observed entropy changes (in 80% ethanol) of ~6 e.u. associated with α-methyl substitution (in passing from *p*-methylbenzyl to 1-phenylethyl chloride), and of ~11 e.u. for α-phenyl substitution (in diphenylmethyl chloride), were found to be roughly correlated with the number of water molecules which could be fitted into a volume equal to that of the substituent. For the corresponding nitrates the closely similar figures (in 90% ethanol) of 8 and 13·5 e.u. respectively (calculated from our *A* values) are found.

Comparison of available data shows that the bimolecular solvolysis rates of the aralphyl nitrates are of the same order of magnitude as those of the corresponding chlorides. In the S_N1 region, however, the nitrates generally have rather higher velocities than the chlorides, whilst *tert.*-butyl nitrate has an exceptionally high value, closely comparable to that of *tert.*-butyl bromide. Since there is only one configuration of the nitrate group which permits free rotation in *tert.*-butyl nitrate it is possible that some steric acceleration of the unimolecular solvolysis may occur in this case. The values of E_A for the nitrates are ~2—3 kcal./mole higher than for the corresponding chlorides, but the activation entropies of the nitrates are also considerably higher (about 2 in log *A*). It is probable that the higher heterolytic bond energy of C–O·NO_2 compared with C–Cl is an important contributory factor in the higher E_A value, whilst the larger *A* factor may be correlated with the higher entropy of the nitrate (35·0) in comparison with that of the chloride (13·2 e.u.) ion ("Chemical and Thermodynamic Properties," Circ. 500, Nat. Bur. Stand., 1951, pp. 53, 21). Thus in neutral solvolysis the organic nitrates exhibit no anomalous behaviour.

(2) *Bimolecular substitution*, S_N2

There are several reasons why the separated rate constants for bimolecular substitution by "hydroxide" * ion in aqueous ethanol are the most difficult to determine and are of low accuracy. In alkaline solution either the $E_{CO}2$ reaction may greatly preponderate (*e.g.*, *p*-nitrobenzyl nitrate) or the bimolecular reaction may be accompanied by a dominant first-order solvolysis which necessitates the use of lengthy computational methods which cause all the errors to accumulate in the k (S_N2) value. This applies especially to *p*-methylbenzyl nitrate in 60% ethanol when the main reaction becomes a unimolecular solvolysis. In such cases rather more favourable conditions are obtained by increasing the relative concentration of the alkali used. The true second-order nature of the corrected k (S_N2) constant is illustrated by the following results in 60% ethanol. (All second-order constants

	$[RNO_3]$	$[OH^-]$	10^5k (S_N2)	10^5k_3 (exp.)
Ph·CH_2·NO_3 at 60°	0·035	0·040	75	120
"	0·051	0·106	76	95
p-C_6H_4Me·CH_2NO_3 at 45°	0·033	0·044	25·0	150
"	0·054	0·098	24·0	85

in this communication are in $mole^{-1}$ l. $sec.^{-1}$). The last column gives the value of the second-order constant for total substitution at zero time, the deviation from k (S_N2) being entirely accounted for by a variable contribution from accompanying solvolysis. The separate values of k (S_N2), corrected for solvent expansion, for the various nitrates investigated are collected in Table 4.

The dual polar requirements of a bimolecular nucleophilic substitution of benzyl nitrate have already been noted. Replacement of a neutral solvent molecule by an anion as the nucleophilic reagent should increase the importance of those polar effects which facilitate electrostriction of the attacking reagent, which was of minor significance in neutral solvolysis. It is therefore not surprising to find that, although nuclear substitution in benzyl nitrate causes only small velocity changes, both an electron-releasing methyl group and electron-attracting bromine now increase k (S_N2), which is at a minimum in the unsubstituted parent. Introduction of a 2-phenyl group reduces the velocity of alkaline hydrolysis of ethyl nitrate [10^5k $(S_N2)^{59·2}$ in 90% EtOH = 4·13; Baker and Easty, *loc. cit.*] about 25-fold, *i.e.*, a much larger effect than in neutral solvolysis.

* Solutions of sodium hydroxide in aqueous ethanol: the equilibrium $HO^- + EtOH \rightleftharpoons H_2O + OEt^-$ (Baker and Neale, *J.*, 1954, 3225) means that the actual nucleophilic reagent is indeterminate.

TABLE 4. *Values of k (S_N2) for the reactions of* OH^- *with* RNO_3 *in x% aqueous* EtOH *at various temperatures.*

Temp.	x	10^5k (S_N2)	Estimated error	Temp.	x	10^5k (S_N2)	Estimated error
		R = Ph·CH_2				R = *p*-C_6H_4Me·CH_2	
60·2°	90	97	± 10%	60·2°	90	194	± 8% E_A = 20·1 kcal./mole
45·0	,,	27·5		45·0	,,	38·3	
30·0	,,	4·6		30·0	,,	8·1	
20·0	,,	1·38		20·0	,,	2·52	
60·2	60	76	± 8% E_A = 19·6 kcal./mole	60·2	60	116	± 25%
45·0	,,	15·8		45·0	,,	25	
30·0	,,	3·7		30·0	,,	5·4	
20·0	,,	1·20		20·0	,,	1·7	
		R = *p*-C_6H_4Br·CH_2				R = Ph·CH_2·CH_2	
20·0	90	3·3	± 20%	60·2	90	0·16	(Preliminary figure)
20·0	60	2·2	± 5%				

Consistently with the requirements of a bimolecular reaction between a negative ion and a neutral molecule in which the charge becomes dispersed in the transition state, increase in the water content of the solvent now causes a small decrease in velocity. This is clearly established by the data in Table 4 and by the more complete range (uncorrected for solvent expansion) for benzyl nitrate given below:

Solvent, x% EtOH	x = 100	90	60	45
10^5k (S_N2)[60·2]	100 *	93	74	50 *

* Part IV, *loc. cit.*

For those nitrates where neither unimolecular solvolysis nor bimolecular carbonyl elimination largely monopolises the reaction course, the relative importance of the bimolecular substitution and carbonyl elimination reactions is shown in Table 5. Electron-

TABLE 5. *Ratio* $100k$ (S_N2)/[k (S_N2) + k ($E_{CO}2$)] *for* RNO_3 *in* x% *aqueous* EtOH *at* 20°.

x	R = CH_2Ph	*p*-C_6H_4Me·CH_2	*p*-C_6H_4Br·CH_2	x	R = CH_2Ph	*p*-C_6H_4Me·CH_2	*p*-C_6H_4Br·CH_2
60	34	66	9·7	90	13	46	3·7

repelling substituents increase, and electron-attracting ones decrease, the proportion of the S_N2 reaction, but it will be seen (Section 3) that the ratio is essentially governed by the much greater sensitivity of the $E_{CO}2$ reaction to structural changes. The dispersal of the negative charge will be greater in the transition state of the $E_{CO}2$ reaction, $\overset{\delta-}{HO}\cdots H\cdots C{=}O\cdots\overset{\delta-}{NO_2}$, than in that of the S_N2 reaction, $\overset{\delta-}{HO}\cdots CH\cdots\overset{\delta-}{O}\cdot NO_2$ and, in harmony with this, it will be noticed that the proportion of substitution increases in the more aqueous solvent, in the same manner as that in which the ratio $E_2/(E_2 + S_N2)$ for olefin elimination in the action of hydroxide ion on, say, *iso*propyl bromide decreases as the water content of the alcohol solvent is increased (Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, pp. 457, 459).

As indicated in Table 2, addition of sodium hydroxide causes no superimposition of any significant second-order reaction to the first-order solvolysis of the other nitrates studied, but certain complexities noticed in the case of diphenylmethyl nitrate are noteworthy, although we can offer no completely satisfactory explanation. Although the presence of 0·04N-sodium hydroxide in 90% aqueous ethanol caused no increase in the solvolytic constant k_1 of this nitrate, a similar concentration of potassium hydroxide produced quite a marked acceleration; the following values exclude any $E_{CO}2$ reaction:

Reagent	10^5k_1 (sec.$^{-1}$) 0°	10°	Reagent	10^5k_1 (sec.$^{-1}$) 0°	10°
90% EtOH	6·06	26·6	90% EtOH + 0·04N-KOH	6·75	28·4
90% EtOH + 0·04N-NaOH	5·93	26·5			

Diphenylmethyl chloride is solvolysed in 100% ethanol at a rate which is independent of alkali concentration (Ward, *J.*, 1927, 2294) but we found that 0·04N-sodium ethoxide increased the rate of solvolysis of the corresponding nitrate in the same solvent:

	10^5k_1 (sec.$^{-1}$)				10^5k_1 (sec.$^{-1}$)		
Reagent	10°	20°	30°	Reagent	10°	20°	30°
100% EtOH	2·80	11·8	45·0	100% EtOH + 0·04N-NaOEt	3·30	13·2	51·0

It was proved by a blank experiment ($10^5k_1^{20} = 11·9$) that the higher figures in the presence of alkali are not due to adventitious absorption of water by the hygroscopic solvent during the necessary additional operations involved in the use of alkali. It is perhaps significant that in the cases where higher velocities were observed in the presence of alkali, and only in these, separation of the alkali-metal nitrate occurred during the reaction. The resultant reduction in the $[NO_3^-]$ might decrease the speed of recombination of R^+ and NO_3^- ions, thus increasing the observed velocity of the rate-determining ionisation $RNO_3 \longrightarrow R^+ + NO_3^-$, but no discontinuity was detected in the reaction rate such as would be expected if this were the correct explanation.

In their examination of alkyl nitrates, Baker and Easty (*loc. cit.*) commented on the very slow rates of hydrolysis by the bimolecular mechanism, by comparison with the corresponding bromides. The more extended series of nitrates now studied makes possible comparison with various other esters of the same aralkyl groups, and it is evident that for both solvolysis and alkaline hydrolysis the rates of the nitrates closely resemble those of the corresponding chlorides. It was tentatively suggested that a possible reason for the slow rate in the case of the nitrates might be a repulsion of the nucleophilic reagent by the negative charge on the oxygen atoms of the nitric ester. The wider comparison now available makes this view untenable since, in all cases, the ratio k_2 (RNO$_3$)/k_2 (RCl) undergoes little change when the reagent is changed from a neutral alcohol molecule to a negatively charged bromide (Baker and Nathan, *J.*, 1936, 236) or hydroxide ion with which, if they were important, such repulsive forces should be very much greater. There is thus nothing abnormal about the slow rates of alkaline hydrolysis observed with some nitric esters.

(3) *The carbonyl-elimination reaction, $E_{CO}2$.*

Reasons were given in Part III (Baker and Neale, *J.*, 1954, 3225) for the belief that the E_{CO} reaction can occur only by a bimolecular mechanism $\overset{\curvearrowright}{X}\ H\!-\!CHR\!-\!O\!-\!\overset{\curvearrowright}{N}O_2 \longrightarrow HX + R{\cdot}CH{:}O + NO_2^-$, and we always find that this reaction is of true second order. This is illustrated by the representative results in Table 6. Except for small variations, partly accounted for by salt effects, the second-order velocity coefficient is evidently independent of concentration. Unlike those of k (S_N2), the values of k ($E_{CO}2$) can be

TABLE 6. *Initial values of* 10^5k ($E_{CO}2$) (*mole*$^{-1}$ *l. sec.*$^{-1}$) *for the alkaline hydrolysis of* RNO_3 *in* x% *aqueous* EtOH.

	R = *m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$; $x = 90$; $T = 0°$.				R = CH_2Ph $x = 60$; $T = 60°$.		R = *p*-$C_6H_4Me{\cdot}CH_2$; $x = 60$; $T = 45°$	
$10^4[RNO_3]$ ...	616	282	387	4·57	344·7	515	335	545
$10^4[NaOH]$ ...	358	361	886	1130	403	1060	440	979
10^5k ($E_{CO}2$) ...	370	361	352	330	189	177	14·7	14·6

determined with considerable accuracy whatever rate law governs the total reaction. This is because of the extreme sensitivity of the colorimetric NO_2^- determinations, a concentration of 3×10^{-5}M being readily determined to an accuracy of $\pm 2\%$.

The separated values of k ($E_{CO}2$) obtained for the various nitrates studied are given in Table 7. The much greater sensitivity of the $E_{CO}2$ reaction to structural changes is immediately apparent.

Baker and Easty (*loc. cit.*) gave theoretical reasons why electromeric effects might predominantly control bimolecular carbonyl elimination from organic nitrates. The limited information then available for alkyl substitution was in harmony with this view,

although disturbances due to inductive effects were also evident. The wider range of results now available makes a re-assessment of the position possible. Values of k ($E_{CO}2$) (mole^{-1} l. sec.$^{-1}$) under comparable conditions of solvent and temperature are given in Table 8. Consideration of the transition stage $\overset{\delta-}{HO}\cdots H\cdots CR{=}O\cdots\overset{\delta-}{NO_2}$ suggests two features which should be primarily concerned with the ease of the carbonyl elimination reaction. They are (1) the positive character of the eliminated hydrogen, *i.e.*, the strength of the nitric ester as a pseudo-acid, and (2) conjugation (or hyperconjugation) of the α-substituent group R with the forming carbonyl double bond.

TABLE 7. *Values of k ($E_{CO}2$) (corr.) in the alkaline hydrolysis of nitric esters* R·NO$_3$.

R	Temp.	Solvent	10^5k ($E_{CO}2$)	R	Temp.	Solvent	10^5k ($E_{CO}2$)
CH_2Ph	60·2°	90% EtOH	847	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	10·0°	90% EtOH	106,000
,, ...	45·0	,,	175	,,	0·0	,,	34,800
,, ...	30·0	,,	31·6	,,	−10·0	,,	10,100
,, ...	20·0	,,	9·24	,,	0·0	60% EtOH	7,400
,, ...	60·2	60% EtOH	183	*o*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	0·0	90% EtOH	24,400
,, ...	45·0	,,	41·0	,,	0·0	60% EtOH	5,180
,, ...	30·0	,,	7·90	*p*-$C_6H_4Br{\cdot}CH_2$ ...	20·0	90% EtOH	85·2
,, ...	20·0	,,	2·45	,,	,,	60% EtOH	20·4
p-$C_6H_4Me{\cdot}CH_2$ ...	60·2	90% EtOH	306	*p*-$MeO{\cdot}C_6H_4{\cdot}CH_2$	20·0	90% EtOH	1·91
,, ...	45·0	,,	61·5	$CHPh_2$	30·0	100% EtOH	159
,, ...	30·0	,,	9·85	,, ...	20·0	,,	52·5
,, ...	20·0	,,	2·90	,, ...	10·0	,,	16·1
,, ...	60·2	60% EtOH	74·2	,, ...	20·0	90% EtOH	31·7
,, ...	45·0	,,	15·0	,, ...	10·0	,,	10·7
,, ...	30·0	,,	2·99	,, ...	0·0	,,	2·98
,, ...	20·0	,,	0·866	CHPhMe	20·0	90% EtOH	0·127
m-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	20·0	90% EtOH	4,560	$Ph{\cdot}CH_2{\cdot}CH_3$ ...	60·2	90% EtOH	0·33
,,	10·0	,,	1,310				
,,	0·0	,,	365				
,,	−10·0	,,	87·4				
,,	0·0	60% EtOH	91·9				

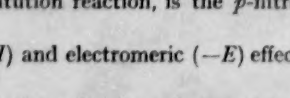
TABLE 8. *Values of* 10^5k ($E_{CO}2$) *for alkaline hydrolysis of* RNO_3 *in* 90% *aqueous* EtOH.

R =	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*o*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$ *	*m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*p*-$C_6H_4Br{\cdot}CH_2$
10^5k ($E_{CO}2$)^{20}	340,000	240,000	4560	85·2
10^5k ($E_{CO}2$)^{60}	—	—	—	—
R =	$CHPh_2$	CH_2Ph	*p*-$C_6H_4Me{\cdot}CH_2$	*p*-$MeO{\cdot}C_6H_4{\cdot}CH_2$
10^5k ($E_{CO}2$)^{20}	31·7	9·24	2·90	1·91
10^5k ($E_{CO}2$)^{60}	—	847	306	—

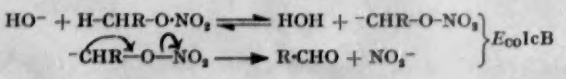
R =	CHPhMe	$Ph{\cdot}CH_2{\cdot}CH_3$	Et †	Pr^i †	CH_3 †
10^5k ($E_{CO}2$)^{20}	0·127	—	—	—	—
10^5k ($E_{CO}2$)^{60}	—	0·33	0·2	0·1	negligible

* Estimated from experiments at 0°. † Baker and Easty (*loc. cit.*).

Electron attraction by the group R by a $-I$, and especially by a $-T$, effect should greatly increase the acid strength of the nitric ester. α-Phenyl groups should thus facilitate the reaction on both counts, whereas alkyl groups, although weakly hyperconjugating with the forming double bond will, by their inductive effects, reduce the positive character of the α-hydrogen by direct action on the C_α to which it is attached. Comparison of benzyl with ethyl nitrate at once reveals that phenyl is approximately 4×10^3 times as efficient as methyl in promoting carbonyl elimination, whilst the very small effect of a β-phenyl substituent (in 2-phenylethyl nitrate) is clear evidence that it is the conjugative effect of phenyl which is important. Introduction of a second α-substituent brings in a statistical factor since there is now only one α-hydrogen for attack by the nucleophilic reagent but, allowing for this, a second α-phenyl (to give diphenylmethyl nitrate) further increases the velocity by only seven-fold, whilst an α-methyl group (to give 1-phenylethyl nitrate) actually reduces the velocity to about 1/40 of the value for benzyl nitrate. Once the essential " phenyl-forming double bond " conjugation is present it would seem that further

polar substituents in the ring function mainly by virtue of their effect on the acid strength of the nitrate. Electron-attracting groups (Br, NO_2) greatly increase and electron-releasing groups (Me, MeO) decrease the rate of the $E_{CO}2$ reaction by altering the electron-density at C_α and hence the ease of fission of the C_α–H bond. The results obtained with such nuclear substitution provide a striking illustration of the importance of polarisability phenomena. *p*-Methoxybenzyl nitrate is simultaneously decomposed by two different reactions with different polar requirements. The strongly electron-demanding substitution reaction (S_Ni) utilises the powerful $+E$ effect of the methoxyl group , causing a large increase in velocity, whereas the concomitant $E_{CO}2$ reaction makes no such demand and it is only slightly impeded by the relatively small mesomeric electron-release of this group. A similar argument is valid for the weaker hyperconjugative effect of a *p*-methyl substituent. The strong acceleration of the $E_{CO}2$ reaction by a *m*-nitro-group shows the importance of the inductive effect in increasing the acid strength of the nitrate, but the real counterpart in carbonyl elimination, of the *p*-methoxy-group in the substitution reaction, is the *p*-nitro-group which, by full operation of both its inductive ($-I$) and electromeric ($-E$) effects  , increases the velocity of the $E_{CO}2$ reaction by a factor of 4×10^4 so that it now becomes the sole reaction. The importance of the electromeric effect of the *p*-nitro-group and, incidentally, the uniformity of the mechanism of the E_{CO} reaction throughout the whole range of nitrates $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}NO_3$ examined, is confirmed by the good straight-line Hammett plot of $\log k/k_0 = 3{\cdot}40\sigma$ which is obtained providing Hammett's higher value 1·27 (which takes into account its tautomeric effect) is used for the *p*-nitro-group.

The evident importance of the acidity of the nitric ester raises the question of the alternative mechanism



in which reaction occurs through the conjugate base. At the moment we have no definite evidence to exclude this possibility, but the isotopic test (Skell and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1661) excluded it in the corresponding olefin-elimination reaction. Our system is, however, one in which such an alternative mechanism is inherently probable (Ingold, *op. cit.*, p. 423, foonote).

A more detailed picture of the effects of substitution on the $E_{CO}2$ reaction results from examination of the Arrhenius parameters. Those available are given in Table 9.

TABLE 9. *Arrhenius parameters for the* $E_{CO}2$ *reaction of* RNO_3 *in* x% *aqueous* EtOH.

R	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	*m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	CH_2Ph		*p*-$C_6H_4Me{\cdot}CH_2$		$CHPh_2$	
x	90	90	90	60	90	60	100	90
E, kcal./mole ...	17·92	20·65	21·80	20·90	22·6	21·16	19·52	18·98
log *A*	13·9	14·1	12·28	10·99	12·28	10·74	11·31	10·7

With nuclear-substituted benzyl nitrates the velocity sequence from the rate constants is confirmed by the Arrhenius E_A values *p*-NO_2 < *m*-NO_2 < H < *p*-CH_3, but the introduction of the polar nitro-group both lowers E_A and increases the entropy term. Introduction of a second α-phenyl group to give diphenylmethyl nitrate does considerably lower the activation energy, and the relatively small increase in the velocity of the $E_{CO}2$ reaction is determined by the simultaneous decrease in log *A*. This may be due to the considerable rigidity likely in the transition state for the formation of benzophenone with both phenyl groups tending to conjugate with the forming double bond. The activation energy is lower in the more aqueous solvent, and the observed *decrease* in velocity is due to the decrease in the entropy term. The most important feature in this reaction is the

destruction of charge, and consequent change in solvation, of the attacking hydroxide ion in the transition state, and the direction and magnitude of both energy and entropy changes are in harmony with the values obtained by Latimer and Slanksky (*J. Amer. Chem. Soc.*, 1940, **62**, 2019) for the heats and entropies of solution of potassium bromide and chloride in aqueous methanol mixtures. As already indicated (p. 621) the greater charge distribution which occurs in the transition state for the $E_{CO}2$ reaction compared with that in the S_N2 reaction causes a greater relative decrease in velocity with increase in the ionising power of the solvent. This is directly confirmed by the following ratios of the velocities of the two reactions for various nitrates, $X{\cdot}C_6H_4{\cdot}CH_2NO_3$, in 90% and 60% ethanol at 20°:

X =	*p*-CH_3	H	*p*-Br	*m*-NO_2 *	*o*-NO_2 *	*p*-NO_2 *
k ($E_{CO}2$), 90%/k ($E_{CO}2$), 60%	3·4	3·8	4·2	4·5	5·2	5·3
k (S_N2), 90%/k (S_N2), 60%	1·5	1·1	1·5	—	—	—

* Estimated from results at 0°.

Increasing electron-attraction in the ring causes higher positive polarity of the α-hydrogen atoms, which will result in greater destruction of charge on the attacking hydroxide ion in the transition state, and this trend is reflected in the more pronounced alteration in rate on passing from 60% to 90% ethanol noted for the nitrates to the right of the above table.

The presence of contemporaneous reactions of different kinetic order means that the percentage of $E_{CO}2$ reaction varies with the concentration of added base and with the solvent and hence bears no *simple* relation to structure. In a medium of low ionising power, such as 90% ethanol, not favourable to solvolytic reaction, the overall picture is given in Table 10. Thus a necessary (but not sufficient) condition for the $E_{CO}2$ reaction to

TABLE 10. *Percentage of $E_{CO}2$ reaction in the weakly alkaline hydrolysis of* RNO_3 *in* 90% *aqueous* EtOH *at* 20°.

R	$E_{CO}2$ (%)	Remarks
p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	>96	From $[\bar{N}O_3]$ at infinity : is probably the sole reaction
m-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	>96	
o-$NO_2{\cdot}C_6H_4{\cdot}CH_2$	100	
p-$C_6H_4Br{\cdot}CH_2$	96	100k ($E_{CO}2$)/[k (S_N2) + k ($E_{CO}2$)]
CH_2Ph	87	
p-$CH_3{\cdot}C_6H_4{\cdot}CH_2$	54	
p-MeO·$C_6H_4{\cdot}CH_2$	0·2	Predominant solvolysis : 100k ($E_{CO}2$)/total reaction
$CHPhMe$	3·0	
$CHPh_3$	1·0	
$Ph{\cdot}CH_2{\cdot}CH_3$	~5	At 60°
Et	2·0	At 30° (Baker and Easty, *loc. cit.*)

constitute a large proportion of the total reaction is that the nitrate should be prone to reaction by the bimolecular mechanism. With nitrates which undergo solvolysis by the unimolecular mechanism the speed of this reaction is such that the $E_{CO}2$ reaction only constitutes a few per cent. of the total reaction. The value of k ($E_{CO}2$) for diphenylmethyl nitrate is actually 3—4 times that for benzyl nitrate, but against this the value of k_1 for the solvolysis (substitution) reaction is 4×10^4 times as great, thus causing a reduction in the proportion of carbonyl elimination from 87% to 1%.

Baker and Neale (Part III, *loc. cit.*) showed that the $E_{CO}2$ reaction with different basic reagents follows the Brönsted law, and hence replacement of an attacking hydroxide ion by the very much weaker base, a water or alcohol molecule, will result in an enormous fall in the reacton rate. Only with a highly reactive compound like *p*-nitrobenzyl nitrate might such solvolytic E_{CO} reaction possibly be detected. The nitrate is so susceptible to attack by alkali, even from glass, that the test had to be conducted in Fluon vessels (Part I). In the solvolysis of a 0·033M-solution in 90% ethanol at 75° only very small amounts of nitrite were detected, but their irregularity suggested no relation to time of reaction, and they most probably arose from slight reduction, by the alcoholic solvent, of the liberated nitric acid. After 36% reaction (96 hr.) the final NO_2^- was only 34×10^{-6}M, which, if significant, would correspond to only 0·3% elimination and k ($E_{CO}2$) =

3×10^{-9} mole^{-1} l. sec.$^{-1}$. An order-of-magnitude calculation based on the relative values of the catalytic coefficients $k_{OH}/k_{H_2O} = 5 \times 10^{10}$ (Bell, "Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 92) suggests that the pseudo-first-order coefficient for carbonyl elimination by water molecules in 90% ethanol at 75° is $\sim 10^{-13}$ sec.$^{-1}$, a rate much too small to detect.

In the alkaline hydrolysis of *m*- and *p*-nitrobenzyl nitrates a marked downward drift was observed in the value of the second-order rate constant as the reaction proceeded. This drift was the more pronounced the lower the initial concentration of alkali. Examination, using the *meta*-isomer, showed that (1) in the presence of a large initial concentration of *m*-nitrobenzaldehyde the velocity coefficient was much smaller but remained constant throughout the run, and (2) that with a large excess (200-fold) of alkali (0·1M) a strictly first-order rate law was observed, showing that retardation by the aldehyde formed was negligible under these conditions. All three nitrobenzaldehydes are soluble in alkali with slow decomposition but are reprecipitated by immediate acidification of the solution, and it is evident that the decreasing second-order coefficient arises simply from the reduction in the concentration of the attacking alkali by the aldehyde produced acting as a neutralising acid. Extrapolation of the velocity coefficient to zero time was therefore necessary.

(4) *Olefin elimination* (E)

Only a few preliminary results have been obtained for the olefin-elimination reaction with 1- and 2-phenylethyl nitrate. The use of an extremely sensitive amperometric method for the determination of styrene (see p. 627) has permitted a reliable estimate of the very small amounts of this olefin formed in the solvolysis of these nitrates. For unimolecular elimination in the solvolysis of 1-phenylethyl nitrate in x% ethanol the percentages of styrene formed are

	x =	90	60		x =	90	60
At 60°	.....	1·19	—	At 20°	.....	0·59	0·2

Hughes *et al.* (*J.*, 1940, 908) found ~0·5% of styrene produced in the solvolysis of the corresponding bromide in 100% ethanol at 55°. The closely similar proportion of olefin in both esters is expected, since it is determined in the subsequent fast reaction of the same carbonium ion in both cases. The effects of temperature and solvent composition are closely similar to those observed with the halides and are doubtless similarly accounted for (Ingold, *op. cit.*, pp. 459, 463).

The limited results obtained for bimolecular olefin elimination with both 1- and 2-phenylethyl nitrates are given, together with those for corresponding bromides for comparison, in Table 11. The facilitating effect of phenyl substitution, especially in the

TABLE 11. *Values of* 10^5k (E_2) *per branch for* RX.

X =	NO_3 [a]	Br	X =	NO_3 [a]	Br
CHPhMe at 20°	0·016	0·79 [c]	Et at 60°	0·08 [b]	1·6 [d]
$Ph{\cdot}CH_2{\cdot}CH_2$ at 60°	8·1	561 [d]	Pr^i at 60°	0·05 [b]	7·6 [d]

[a] In 90% EtOH. [b] Baker and Easty, *loc. cit.* [c] In 100% EtOH at 25°. [d] In 100% EtOH at 55°.

β-position, is evident. With 1-phenylethyl nitrate in 90% ethanol at 20° there is approximately 4% of carbonyl and 1% of olefin formation, but in the alkaline hydrolysis of 2-phenylethyl nitrate in the same solvent, at 60°, approximately 94% of the total reaction is olefin elimination, 4% carbonyl elimination, and only 2% substitution, the corrected values of the rate coefficients being 10^5k (E_2) = 8·1, 10^5k ($E_{CO}2$) = 0·345, and 10^5k (S_N2) = 0·17; all in mole^{-1} l. sec.$^{-1}$.

EXPERIMENTAL

Preparation of Materials.—We were unaware of the homogeneous method for the preparation of nitrates from the halides and silver nitrate (Ferris *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 4078) until quite late in this investigation and hence most of our nitrates were prepared by the

heterogeneous reaction in ether. Benzyl nitrate, b. p. 78°/3 mm., n_D^{20} 1·5204, was prepared as described in Part III (*loc. cit.*) (Found: C, 54·8; H, 4·4. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6%). Hydrolysis showed 100% purity by both acid and nitrate-ion determinations.

p-*Methylbenzyl nitrate.* The bromide, m. p. 35·8°, in ether was treated at 0° with powdered silver nitrate, then kept at room temperature for 12 hr., and finally refluxed at 70° for 6 hr. Purification by fractionation and partial freezing gave a sample, b. p. 78°/0·6 mm., n_D^{20} 1·5178 (Found: C, 57·0, 57·4, 58·2; H, 4·75, 4·9, 5·3; N, 8·05, 7·9. Calc. for $C_8H_9O_3N$: C, 57·5; H, 5·4; N, 8·4%). The mean of six complete solvolyses under different reaction conditions showed 99·31% purity, and whenever infinity values were not available this factor was used to correct the initial weight of ester used. The trace of impurity was shown to be without effect on the kinetics.

Diphenylmethyl nitrate. An ethereal solution of the chloride, b. p. 115—116°/0·4—0·5 mm., was shaken in the dark at room temperature with finely powdered silver nitrate and a little calcium carbonate, until freedom from unreacted chloride was established. The pale yellow liquid obtained by evaporation of the filtered ethereal solution, solidified at −70°. The *nitrate* crystallised from ligroin (b. p. 40—60°) in colourless needles, m. p. 36·7—37·2° (Found: C, 68·2; H, 4·7; N, 5·9. $C_{13}H_{11}O_3N$ requires C, 68·15; H, 4·8; N, 6·1%). Complete solvolysis showed 100% purity (cf. Baker and Heggs, *Chem. and Ind.*, 1954, 464).

p-*Methoxybenzyl nitrate.* Similarly obtained from the chloride (prepared from the alcohol by Swain and Langsdorf's method, *J. Amer. Chem. Soc.*, 1951, 73, 2813) was an orange oil which decomposed when molecular distillation was attempted but was obtained reasonably pure by crystallisation from ether at −70°. It was used immediately for kinetic experiments, the concentration being determined from infinity values.

o-*Nitrobenzyl nitrate,* by refluxing the chloride with finely powdered silver nitrate in ether for 7 days, was obtained as a red oil. Extraction of the oil with ligroin gave a solution which deposited white needles after being kept at −70°. Two further crystallisations from the same solvent gave a 10% yield of the nitrate, m. p. 28° (Found: C, 42·6; H, 3·3; N, 14·1. $C_7H_6O_5N_2$ requires C, 42·4; H, 3·0; N, 14·1%).

m-*Nitrobenzyl nitrate,* pale yellow crystals, m. p. 42·5—43·0° (Found: C, 42·6; H, 3·3; N, 13·9%), and p-*nitrobenzyl nitrate,* m. p. 68·2° (Found: C, 42·5; H, 2·9; N, 13·9%), were readily prepared in good yields by a similar method. p-*Bromobenzyl nitrate* was similarly obtained from the bromide as a colourless oil, the ligroin (b. p. 40—60°) solution of which deposited crystals at −70°. Recrystallisation under the same conditions gave the pure nitrate, m. p. 17°, to a colourless oil, n_D^{20} 1·5639 (Found: C, 36·45; H, 2·6; N, 5·95; Br, 34·7. $C_7H_6O_3NBr$ requires C, 36·2; H, 2·6; N, 6·0; Br, 34·45%).

1-*Phenylethyl nitrate.* The (±)-bromide, b. p. 38°/0·2 mm., n_D^{20} 1·5622 (20 g.), dissolved in dry, redistilled acetonitrile (50 c.c.), was added slowly to a solution of silver nitrate (30 g.) in acetonitrile (50 c.c.) at 0°, and the mixture kept at room temperature for 12 hr., the solvent was then removed *in vacuo* from the filtered solution. The residue separated into two layers and the upper layer was fractionated to constant refractive index to yield the *nitrate,* b. p. 49°/0·2 mm., n_D^{20} 1·5092 (Found: C, 57·6; H, 5·4; N, 8·4. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%). By a similar method the isomeric bromide, b. p. 38°/0·2 mm., n_D^{20} 1·5580, was converted into 2-*phenylethyl* (*phenethyl*) *nitrate,* b. p. 65°/0·5 mm., n_D^{20} 1·5162 (Found: C, 57·9; H, 5·3; N, 8·4%). Neither of these nitrates could be induced to crystallise at temperatures down to −70°.

Aqueous-alcoholic solvents were prepared from 100% ethanol, dried as described in Part III (*loc. cit.*); "*x* vol. % ethanol" has the same meaning as in previous parts of this series.

Kinetic Techniques and Analytical Processes.—Kinetic techniques and analytical processes were essentially those described in Part III. In gravimetric determinations of benzaldehyde as its 2 : 4-dinitrophenylhydrazone, nitrous acid interferes. Nitrogen evolved when removal with sulphamic acid prior to precipitation is used causes difficulties by adhering tenaciously to the precipitate, and the best method was found to be the use of a very large excess (200 ml. per mmole of aldehyde) of the reagent (0·125 g. of 2 : 4-dinitrophenylhydrazine in 2·5 ml. of concentrated sulphuric acid diluted to 50 ml. with water). By this technique 99·5% recovery of benzaldehyde was effected even in presence of large amounts of nitrite.

Determination of Styrene.—The production of alkyl aryl ketones in our reactions means that determination of olefin by addition of excess of bromine and back titration is likely to be inaccurate because of side reactions. We have therefore used a direct bromine-titration method, using an electrometric method to find the equivalence point (Kolthoff and Bovey, *Ind. Eng. Chem. Anal.*, 1947, 19, 498). We found Kolthoff's original procedure quite satisfactory and, in

fact, addition of mercuric chloride actually decreased the rate of attainment of equilibrium in the cell after each addition of the bromate–bromide solution.

Methanol for the titrating medium was treated with bromine for 12 hr., excess of bromine was destroyed by zinc dust, and the decanted solution was distilled through a Dufton column, the last 15% being rejected. The olefin-containing sample (2 ml.) was added to 30 ml. of the titrating medium (methyl alcohol, 750 ml.; water, 250 ml.; conc. HCl, 100 ml.; "AnalaR" potassium bromide, 10 g.), and the mixture kept at 0° during titration. The cathode consisted of a 3-cm. piece of 0·5-mm. diameter platinum wire bent into a circle and rotating at 1000 rev./min. The anode was a square piece of platinum with surface area of ~0·5 cm.². A polarising voltage of 0·1 v was applied to these by means of a U2 dry cell in series with a high resistance and connected to a radio-potentiometer. The current between the electrodes was measured with a micro-ammeter fitted with suitable shunts, maximum sensitivity being 100 divisions per micro-amp. The solution was titrated with either 0·00017 or 0·0017M-potassium bromate which was 0·1M with respect to potassium bromide. As the end-point was approached 30 sec. were allowed for the attainment of equilibrium after each small addition of the bromate–bromide solution. Blanks were always carried out on the titrating medium before the addition of the sample. The possible disturbing effects of various materials which might be present were tested, and the reliability of the method was established by the following results.

Amperometric determination of styrene.

Added material	Styrene, mg.: taken	found	Error, %	Added material	Styrene, mg.: taken	found	Error, %
Nil	0·196	0·199	+1·4	2 Ml. 0·03M-KNO_3	0·4950	0·4941	−0·2
,,	0·196	0·203	+3·8	5 Mg. Ph·COMe	,,	0·4967	+0·3
,,	0·4950	0·4957	+0·1	16 Mg. Ph·CHMe·NO_3 *	,,	0·5052	+2·0
,,	0·4950	0·4957	+0·1	+2 ml. 0·025M-KNO_3			
2 Ml. 0·025M-KNO_3	,,	0·4963	+0·3	5 Mg. Ph·COMe	,,	0·4977	+0·5
1 Ml. 0·025M-KNO_3	,,	0·4989	+0·8	+2 ml. 0·030M-KNO_3			

* Ph·CHMe·NO_3 was slightly impure and may have contained a trace of unsaturated material.

Calculation of Rate Constants.—Solvolysis constants k_1 were calculated by the usual first-order rate equation, the initial concentration being determined either by direct weighing or from the infinity values, and were checked periodically by Guggenheim's method (*Phil. Mag.* 1926, **2**, 538). The two procedures gave values agreeing within the experimental error. To illustrate the accuracy and the agreement between $[H_3O^+]$ and $[NO_3^-]$ produced, alternate determinations up to 95% reaction in the solvolysis of 0·02872M-benzyl nitrate in 60% EtOH at 45° are recorded below. In alkaline hydrolyses four methods were used to extract the separate values of k (S_N2) and k ($E_{CO}2$) from the total reaction, followed by determination of loss of alkalinity or production of nitrate, and nitrite.

Time (hr.)	14·25	21·5	38·1	51·5	69·25	93·5	185·5	194·1	213·6	254·5
$10^3[H_3O^+]$	4·51	6·52	10·42	13·04	16·14	19·32	25·56	25·81	26·43	27·24
$10^3[NO_3^-]$	4·81	6·61	10·55	13·21	16·42	19·70	25·86	26·55	26·80	27·41
10^4k_1, sec.$^{-1}$	3·32	3·32	3·28	3·26	3·31	3·31	3·30	3·27	3·29	3·23

Mean (of 20 determinations) 10^4k_1 = 3·31 sec.$^{-1}$; by Guggenheim's method 3·34 sec.$^{-1}$.

(1) Hughes, Ingold, and Shapiro's method (*J.*, 1936, 51) was used when the reaction was predominantly of second order. The total second-order rate constant k_2 was determined from $k_2 = {}^1k_2 - k_1/(b - x) + t \cdot \mathrm{d}\,{}^1k_2/\mathrm{d}t$, where ${}^1k_2$ is the experimental integrated second-order rate constant and b is the initial concentration of base. The last term was usually evaluated graphically. The proportion of the reaction x_1 proceeding by the first-order path was then determined from the relationship

$$x_1 = (k_1/k_2)\ \ln\{(k_1/k_2) + b\ [(k_1/k_2) + b - x]\}$$

and hence the total amount of bimolecular reaction was found by difference. The value of the constant for total bimolecular reaction was then split into k (S_N2) and k ($E_{CO}2$) according to the proportion of nitrite produced.

(2) A much more rapid and simplified treatment was to obtain k ($E_{CO}2$) by direct multiplication of ${}^1k_2$ by the carbonyl elimination fraction of the *total* reaction, *i.e.*, k ($E_{CO}2$) = ${}^1k_2[NO_2^-]/x$. The value ${}^1k_2 - k$ ($E_{CO}2$) = k_2' then gives the total second-order constant for substitution

(including solvolysis), whence $k\ (S_N2) = k_2' - (k_1/\text{mean}[OH^-])$. It can be shown that this simplified method is valid when $(b - x)$ changes only slightly, and hence more accurate values values result when rather higher initial concentrations of alkali are used. When solvolysis is important the values of $k\ (E_{CO}2)$ tended to drift downward slightly towards the end of the run and were always extrapolated to zero time. In practice, it was repeatedly found that this method gave the same values for $k\ (E_{CO}2)$ and $k\ (S_N2)$ as those obtained by the more rigorous but much more laborious method (1) and hence the simplified method was generally employed.

The following typical results for the hydrolysis of 0·05148M-benzyl nitrate with 0·1056M-potassium hydroxide in 60% EtOH at 60·2° show the equivalence of $[H_3O^+]$ and $[NO_3^-] + [NO_2^-]$ and the values of $k\ (S_N2)$ and $k\ (E_{CO}2)$ obtained by methods (1) and (2).

Time (min.)	13	21	34	38	42	46	50
$10^3[NO_3^-]$	2·75	5·61	7·94	8·14	8·78	9·49	9·90
$10^3[NO_2^-]$	7·28	10·45	14·37	15·30	16·35	17·16	17·81
$10^3([NO_3^-] + [NO_2^-])$	10·03	16·06	22·31	23·44	25·13	26·65	27·71
$10^3[H_3O^+]$	10·88	15·40	21·80	23·10	24·62	26·69	27·36
$10^3k\ (E_{CO}2)$ (1)	1·75	1·78	1·77	1·76	1·77	1·77	1·73
$10^3k\ (E_{CO}2)$ (2)	1·75	1·78	1·79	1·77	1·78	1·78	1·75
$10^3k\ (S_N2)$ (1)	0·79	0·72	0·78	0·74	0·74	0·78	0·78
$10^3k\ (S_N2)$ (2)	0·79	0·72	0·76	0·73	0·73	0·77	0·76

Time (min.)	55	60	66	73	90	113	∞
$10^3[NO_3^-]$	—	10·85	11·18	11·82	13·12	14·57	19·08
$10^3[NO_2^-]$	18·89	19·90	20·80	22·00	23·66	26·00	32·70
$10^3([NO_3^-] + [NO_2^-])$	—	30·75	31·98	33·82	36·78	40·57	51·78
$10^3[H_3O^+]$	28·74	30·28	31·84	33·40	36·40	39·83	51·79
$10^3k\ (E_{CO}2)$ (1)	1·74	1·76	1·75	1·76	1·70	1·73	—
$10^3k\ (E_{CO}2)$ (2)	1·76	1·78	1·78	1·79	1·73	1·76	—
$10^3k\ (S_N2)$ (1)	0·75	0·76	0·77	0·75	0·75	0·73	—
$10^3k\ (S_N2)$ (2)	0·73	0·74	0·74	0·72	0·72	0·74	—

Whence the mean values, after correction for solvent expansion, are $10^3k\ (E_{CO}2) = 1·83$; $10^3k\ (S_N2) = 0·76$ l. mole^{-1} sec.$^{-1}$.

(3) When the only assumption made is that the carbonyl elimination reaction is always bimolecular, we have $d[NO_2^-]/dt = k\ (E_{CO}2)(a - x)(b - x)$, whence $k\ (E_{CO}2) = [NO_2^-]_0^t/\int_0^t(a - x)(b - x)\ .\ dt$. The numerator was obtained directly from nitrite determinations and the denominator was evaluated graphically. Again a tedious method, it was used only to check the validity of values obtained by other methods.

(4) When the reaction was mainly of first order a method similar to (2) was employed; although strictly valid only when there is $\not>1\%$ bimolecular reaction, it was found to give identical values with those obtained by rigorous methods even when there was 10% of carbonyl elimination. If $^1k_1$ is the experimental, integrated, first-order constant, then the value of $k\ (E_{CO}2)$ was obtained by multiplying it by the carbonyl-elimination fraction of the total reaction and dividing by the mean $[OH^-]$. Again, the value was extrapolated to zero time.

Time (min.)	0	35·9	79·3	125·5	192·7	243·8
$[OEt^-]$	6·638	6·200	5·664	5·182	4·542	4·180
10^3k_1	—	(3·70)	3·92	3·90	3·95	3·84
NO_2^-, %	—	16·8	15·78	15·85	14·53	14·34
$10^1k\ (E_{CO}2)$ (3)	—	1·54	1·59	1·66	1·63	1·63
$10^1k\ (E_{CO}2)$ (4)	—	1·54	1·59	1·66	1·63	1·61

Time (min.)	303·5	363·5	423·0	487·5	580·7	1458
$[OEt^-]$	3·780	3·384	3·082	2·800	2·440	1·125
10^3k_1	3·80	3·85	3·82	3·80	3·80	3·77
NO_2^-, %	14·18	13·30	12·75	12·68	12·03	10·09
$10^1k\ (E_{CO}2)$ (3)	1·66	1·63	1·58	1·61	1·59	—
$10^1k\ (E_{CO}2)$ (4)	1·64	1·62	1·59	1·62	1·60	1·55

Whence $10^1k\ (E_{CO}2) = 16·1$ mole^{-1} l. sec.$^{-1}$.

The following results for the hydrolysis of 0·0380M-diphenylmethyl nitrate with 0·04372M-sodium ethoxide in 100% EtOH at 10° illustrate the application of methods (3) and (4) when the main substitution reaction is of first order. The $[OEt^-]$ is expressed in ml. of 0·01009N-sulphuric acid per 1·597-ml. sample.

Treatment of a more difficult case, when solvolysis accounts for only about 60% of the total

reaction, is illustrated by the following results for the alkaline hydrolysis of 0·0540M-*p*-methylbenzyl nitrate with 0·09793M-potassium hydroxide in 60% aqueous EtOH at 45°.

Time (min.)	$10^3[H_3O^+]$, mole l.$^{-1}$	$10^5 . {}^1k_1$, sec.$^{-1}$	$10^4 . {}^1k_2$, mole^{-1} l. sec.$^{-1}$	NO_2^-, %	10^4k ($E_{CO}2$) (4)	(2)	(3)	10^5k_1, sec.$^{-1}$	10^4k (S_N2)	10^4k (S_N2)
30	8·04	9·27	10·10	14·51	1·45	1·47	1·45	9·20	2·72	2·60
55	13·11	8·75	9·82	14·78	1·44	1·45	1·46	8·62	2·29	2·13
80	18·02	8·82	10·20	14·16	1·43	1·44	1·43	8·64	2·60	2·57
105	22·01	8·67	10·36	13·85	1·41	1·43	1·42	8·43	2·49	2·27
140	26·70	8·52	10·58	13·68	1·40	1·45	1·42	8·20	2·45	2·20
170	30·29	8·51	10·89	13·58	1·42	1·48	1·44	8·12	2·51	2·24
200	33·46	8·52	11·21	13·03	1·39	1·46	1·41	8·07	2·65	2·35
240	36·55	8·52	11·42	12·88	1·37	1·47	1·40	7·95	2·68	2·46
280	39·33	8·33	11·78	12·41	1·35	1·46	1·40	7·70	2·45	2·30
320	41·49	8·24	12·08	12·48	1·36	1·51	1·39	7·51	2·24	2·23
400	44·71	8·18	12·40	11·98	1·31	1·47	1·36	7·19	(1·93)	2·14
440	46·75	8·18	13·65	11·79	1·33	(1·61)	1·37	7·7	(1·97)	2·30

The expected drifts in ${}^1k_1$ and ${}^1k_2$ due to the superimposition of first- and second-order reactions are obvious. The values of k ($E_{CO}2$) in the three columns have been calculated by the methods shown at the head. Substitution constants in the last column have been calculated by multiplying ${}^1k_1$ by the fraction of substitution reaction and subtraction of the solvolysis constant to give a value accounted for by second-order substitution, and division of this by the mean [OH^-] to give k (S_N2). The values of k (S_N2) in col. 10 were evaluated from the equation $k_1 = {}^1k_1 + t \,.\, d{}^1k_1/dt - [k\ (S_N2) + k\ (E_{CO}2)]\ [OH^-]$, where k_1 is the instantaneous first-order rate constant, the values of which are listed in col. 9. The final corrected values are $10^5k\ (E_{CO}2) = 14·9$ and $10^5k\ (S_N2) = 24$ mole^{-1} l. sec.$^{-1}$.

The hydrolysis of 0·043M-1-phenylethyl nitrate with 0·093M-sodium hydroxide in 90% aqueous EtOH at 20° illustrates a run in which both carbonyl and olefin elimination occur. The [OH^-] is expressed in ml. of 0·01009N-sulphuric acid per 1·007-ml. sample:

Time (hr.)	21·25	33·06	45·5	56·83	72·00	99·5	127·5	
[HO_2^-]	0·88	1·30	1·68	2·00	2·39	2·95	3·29	4·31
NO_2^- (%)	3·89	3·71	3·53	3·48	3·31	3·08	3·12	—
Ph·CH:CH_2 (%)	—	1·02	1·04	—	1·07	0·99	—	—
$10^6 {}^1k_1$ (sec.$^{-1}$)	3·01	3·02	3·02	3·05	3·12	3·22	3·14	—
10^6k ($E_{CO}2$)	1·30	1·27	1·24	1·27	1·29	1·25	1·26	—
10^7k ($E2$)	—	1·5	1·6	—	1·8	1·6	—	—

Whence $10^5k\ (E_{CO}2) = 0·127$ and $10^7k\ (E2) = 1·6$ mole^{-1} l. sec.$^{-1}$.

${}^1k_1$ is calculated with the usual integrated first-order equation with use of the experimental infinity value as initial concentration: k ($E_{CO}2$) is computed by method (4). The value of k ($E2$) is estimated by use of the expression $k\ (E2) = {}^1k_1\{\%\ \text{styrene} - 0·59\}/100$ mean[OH^-] (since 0·59% of styrene is produced in solvolysis) and is, of course, subject to a moderately large error (~30%).

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The Synthesis of Some N*-Hydroxyimides.*

By D. E. Ames and T. F. Grey.

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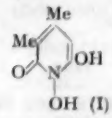
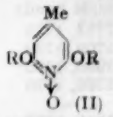
N-Benzyloxyimides, prepared by heating benzyloxyamine with succinic, glutaric, αβ-dimethylglutaconic, and other dibasic acids, have been catalytically hydrogenated to give *N*-hydroxyimides, the structures of which have been examined by measurements of infra-red and ultra-violet spectra and of pK_a values.

The antibiotic aspergillic acid is a pyrazine cyclic hydroxamic acid (Dutcher, *J. Biol. Chem.*, 1947, **171**, 321) and more recent work has shown that analogous pyridine and quinoline derivatives also possess antibacterial properties (Newbold and Spring, *J.*, 1948, 1864; Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2091; Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67; Lott and Shaw, *ibid.*, p. 70). We have now synthesised the related hydroxamic acid (I).

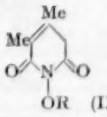
Newbold and Spring (*loc. cit.*) prepared 1-hydroxypyrid-2-one by hydrolysis of 2-methoxypyridine *N*-oxide, and an analogous method employing a dimethoxypyridine *N*-oxide was therefore first examined. 2 : 6-Dimethoxy-4-methylpyridine (Ames, Bowman, and Grey, *J.*, 1953, 3008) with perbenzoic acid gave a small yield of the *N*-oxide (II; R = Me) but attempts to demethylate the latter resulted in decomposition. We next attempted to prepare the dibenzyloxypyridine *N*-oxide (II; R = CH_2Ph), catalytic debenzylation of which should be possible (cf. Shaw, *loc. cit.*). 2 : 6-Dibenzyloxy- and



(I)



(II)



(III)

$HO_2C{\cdot}[CH_2]_n{\cdot}CO{\cdot}NH{\cdot}OR$ (IV)

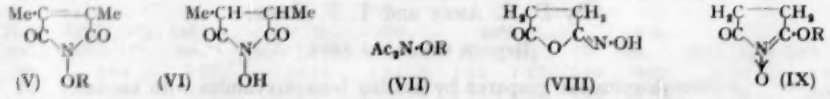
2 : 6-dibromo-4-methylpyridine could not be converted into the *N*-oxides, however, although in both cases more than 1 mol. of perbenzoic acid was consumed. The difficulty of preparing *N*-oxides from 2 : 6-disubstituted pyridines has been indicated by Gilman and Edward (*Canad. J. Chem.*, 1953, **31**, 457). The high consumption of perbenzoic acid in the present case may be analogous to the behaviour of alkoxybenzenes (Friess, Soloway, Morse, and Ingersoll, *J. Amer. Chem. Soc.*, 1952, **74**, 1305).

The compound (I) was synthesised by condensation of αβ-dimethylglutaconic acid with benzyloxyamine followed by catalytic hydrogenation of the resulting *N*-benzyloxyimide (III; R = CH_2Ph). The rearrangement of the intermediate (III; R = H) is shown by physical measurements (see below).

Similar use of benzyloxyamine has also provided convenient syntheses of other *N*-benzyloxy- and *N*-hydroxy-imides. Succinic, glutaric, α-dodecylglutaric, and αβ-dimethylmaleic anhydride in benzene give *N*-benzyloxy-succinamic and -glutaramic acids (IV; R = CH_2Ph, $n = 2$ and 3 respectively) and thence the corresponding hydroxamic acids (IV; R = H). Similarly, the benzyloxyimides furnished the corresponding *N*-hydroxyimides; in the case of (V; R = CH_2Ph), complete hydrogenation gave the compound (VI) but, under different conditions, the semihydrogenation product (V; R = H) could be isolated.

Maleic anhydride in benzene reacted with benzyloxyamine giving *N*-benzyloxymaleinamic acid but repeated attempts to obtain the *N*-benzyloxyimide by thermal dehydration failed. Treatment of *N*-benzyloxymaleinamic acid with thionyl chloride and then pyridine, however, gave a crystalline product which appeared to be the benzyloxyimide, although the light-absorption properties were rather anomalous (see below). Attempts to debenzylate this product by catalytic hydrogenation and by sodium and liquid ammonia were unsuccessful. The dehydration of *N*-benzyloxymaleinamic acid by boiling acetic anhydride was also attempted, but the product was *NN*-diacetyl-*O*-benzylhydroxylamine (VII; R = CH_2Ph) which was also prepared directly from benzyloxyamine. Catalytic

debenzylation of this material yielded the hitherto unknown *NN*-diacetylhydroxylamine (VII; R = H).



The *N*-benzyloxy- and *N*-hydroxy-amides show the expected infra-red absorption bands (Table 1). The imides have infra-red spectra (Table 2) similar to those of unsubstituted and *N*-alkyl-imides with bands at *ca.* 1700 and 1760 cm.$^{-1}$. The former is always the more intense; in several cases the latter band occurs at unusually high frequency (above 1780 cm.$^{-1}$; cf. Randall, Fowler, Fuson, and Dangl, *op. cit.*, p. 20). The close similarity between the spectra of *N*-benzyloxy- and *N*-hydroxy-succinimide and

TABLE 1. *Absorption spectra in region* 1450—1900 *cm.*$^{-1}$.

Bands	Amide	Phenyl	Carboxy	Other bands
N-Benzyloxybenzamide †	1653, 1511	1580, 1484	—	—
NN'-Dibenzyloxy-α-dodecylglutaramide	1656, 1515	•	—	—
N-Benzyloxysuccinamic acid	1653, 1536	1499	1727	1553, 1517
N-Benzyloxyglutaramic acid	1658, 1522	•	1694	—
N-Benzyloxymaleinamic acid	1639, 1534	—	1709	1567
N-Hydroxysuccinamic acid	1664, 1567	—	1709	1621
N-Hydroxyglutaramic acid	1634, 1541	—	1718	—

• No bands detected. All in Nujol. † Beckmann, *Ber.*, 1893, **26**, 2633.

TABLE 2. *Absorption spectra in region* 1450—1900 *cm.*$^{-1}$.

	Imide bands	Other bands
N-Benzyloxysuccinimide	1712, 1779	—
N-Hydroxysuccinimide	1709, 1789	1511, 1692
N-Hydroxy-αβ-dimethylsuccinimide	1695, 1783	1495
N-Pentylsuccinimide [a]	1706, 1770	—
N-Acetoxysuccinimide	—	1754,[b] 1779, 1802, 1832
N-Bromosuccinimide	1718, 1776	1821
N-Benzyloxyglutarimide [a]	1715, 1754	—
N-Hydroxyglutarimide	1672, 1742	—
N-Benzyloxy-α-dodecylglutarimide	1701, 1736	—
α-Dodecyl-*N*-hydroxyglutarimide	1704, 1733	1468
β : β : *N*-Trimethylglutarimide	1672, 1727	—
N-Benzyloxymaleinimide	1721, 1733	—
N-Benzyloxy-αβ-dimethylmaleinimide	1724, 1783	—
N-Hydroxy-αβ-dimethylmaleinimide	1730, 1792	1667
α : β : *N*-Trimethylmaleinimide	1715, 1770	1504, 1536
N-Benzyloxy-αβ-dimethylglutaconimide	1678, 1724	1495
α : β : *N*-Trimethylglutaconimide	1678, 1709	1645
(I) or (X)	—	1466, 1518, 1587, 1637
6-Methoxy-1 : 4-dimethylpyrid-2-one [c]	—	1531, 1580, 1656
2 : 6-Dimethoxy-4-methylpyridine *N*-oxide	—	1585, 1623, 1736,[b] 1779 [b]
NN-Diacetyl-*O*-benzylhydroxylamine	— 1721	1464
NN-Diacetylhydroxylamine	1715, 1799	1608
ON-Diacetylhydroxylamine [d]	—	1534, 1664, 1802

[a] Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949, p. 172. [b] Acetate band. [c] In $CHCl_3$ (others in Nujol). [d] Ames, Bowman, and Grey, *loc. cit.* [e] Very weak bands which may be due to some impurity. [f] Prepared by Hantzsch's method (*Ber.*, 1892, **25**, 701).

of the *N*-pentyl compound confirms these structures and excludes the alternative (VIII) (cf. Orndorff and Pratt, *Amer. Chem. J.*, 1912, **47**, 99). The spectrum of *N*-acetoxysuccinimide, however, shows some anomalous features: although the very strong acetate band (1754 cm.$^{-1}$) has some masking effect, the apparent absence of the imide bands is unexpected; the maxima observed at 1779, 1802, and 1832 cm.$^{-1}$ are unexplained. (*N*-Bromosuccinimide similarly shows a band at 1821 cm.$^{-1}$.) Despite these results the acetoxy-imide structure appears to be more satisfactory than the possible alternative (IX; R = Ac) in view of the low-intensity ultra-violet light absorption (Table 3).

In the case of the αβ-dimethylglutaconic acid derivatives, there is a striking difference between the spectra of the *N*-benzyloxy-imide and of the derived debenzylation product.

TABLE 3. *Ultra-violet light absorption data (95% ethanol solutions) and pK_a values.*

	R = CH_2Ph			R = H		
	$\lambda_{max.}$ (Å)	ε	pK_a	$\lambda_{max.}$ (Å)	ε	pK_a
$HO_2C{\cdot}[CH_2]_2{\cdot}CO{\cdot}NH{\cdot}OR$	2520	176	4·6 [a]	—	—	4·5 [a]
	2580	222	10·2	—	—	9·6
	2640	191				
	2680	127				
$HO_2C{\cdot}[CH_2]_3{\cdot}CO{\cdot}NH{\cdot}OR$	2080	10,800	4·7 [a]	<2100	>1400	4·6 [a]
	2520	164	10·2	—	—	9·6
	2580	218				
	2640	182				
	2680	120				
$HO_2C{\cdot}CH{:}CH{\cdot}CO{\cdot}NH{\cdot}OR$	2100	18,000	3·8 [a]	—	—	—
	2750	5400	10·0			
$CH_2{\cdot}CO$ >N·OR $CH_2{\cdot}CO$	2060	22,700	—	<2050	>7900	6·0 [a]
	2460	512	—	2655	625	
	2520	336				
	2575	342				
	2630	299				
	2690	208				
$CH_3{\cdot}CH{\cdot}CO$ >N·OR $CH_3{\cdot}CH{\cdot}CO$	—	—	—	2650	1670	7·2 [b]
CH_2(CH₂·CO >N·OR)(CH₂·CO)	2090	19,000	—	2160	9700	7·6 [a]
	2520	298				
	2580	319				
	2630	280				
	2690	171				
CH_2(CH₂·CO >N·OR)(CH·CO) n-$C_{12}H_{23}$	2110	15,800	—	2170	9000	10·5 [b]
	2550 [a]	278				
CH·CO ‖ >N·OR CH·CO	2880	14,000	—	—	—	—
MeC·CO ‖ >N·OR MeC·CO	2175	16,700	—	2270	16,800	8·5 [b]
	2250 [a]	14,500	—	2300	17,000	
$Ac_2N{\cdot}OR$	2130	15,200	—	2220	5400	—
Benzyloxyamine	2090	7200	—	—	—	—
	2580	203				
	2640	162				
N-Benzyloxybenzamide	<2050	>18,000	—	—	—	—
	2160 [a]	13,500				
NN'-Dibenzyloxy-α-dodecylglutaramide	2070	22,000	—	—	—	—
	2520	393				
	2580	507				
	2640	430				
	2680	283				
α : β : *N*-Trimethylmaleinimide	2230	16,600	—	—	—	—
	2280	16,700				

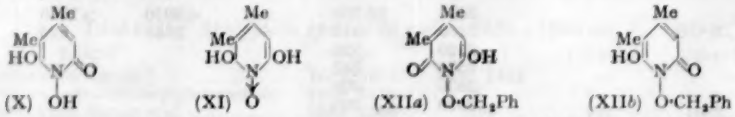
[a] Inflexion.

	95% Ethanol		0·1N-HCl		Alkali (pH 8·9)		
	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	pK_a
(III; R = CH_2Ph)	2440	8500	2565	6400	2400	7400	5·8 [a]
	3275	8900	3020	720	3240	12,900	
(I) or (X)	2400	5100	2165	11,400	3050	9100	5·05 [a]
	3130	7600	2600	4400	—	—	10·35
(II; R = Me)	2285	6900	2290	4100	2280	5400	—
	2925	7100	2910	6400	2915	6200	—
α : β : *N*-Trimethylglutaconimide	—	—	—	—	—	—	6·6 [b]

[a] In water. [b] In water–methanol (1 : 1). [c] In water–dimethylacetamide (1 : 1).

The former shows imide bands very close to those of the *N*-methyl-imide but the latter has no absorption maxima in that region, the spectrum closely resembling that of 6-methoxy-1 : 4-dimethylpyrid-2-one, and it is therefore formulated as (I) or (X). The alternative (XI) is not excluded by the infra-red spectrum but is considered unlikely (see p. 634).

The ultra-violet absorption spectra (Table 3) of most of the *N*-benzyloxy-compounds show the low-intensity absorption band at *ca.* 2600 Å, with fine structure, due to the benzyl group. *N*-Benzyloxymaleinamic acid and *N*-benzyloxymaleinimide, however, unexpectedly exhibit intense maxima at *ca.* 2800 Å, presumably owing to interaction between the two chromophores. *N*-Hydroxyglutaramic acid shows only low-intensity absorption above 2100 Å, but *N*-hydroxyglutarimide and α-dodecyl-*N*-hydroxyglutarimide have absorption maxima of high intensity at *ca.* 2150 Å. *N*-Hydroxysuccinimide and *NN*-diacetylhydroxylamine also absorb fairly strongly at this wave-length. It is suggested that this effect may be due to the presence of hydroxy-*N*-oxide (*e.g.*, IX) in equilibrium with the *N*-hydroxyimide form in solution. The absorption spectra indicate that the compound (III; R = CH_2Ph) is enolised in solution, probably giving an equilibrium mixture of (XII, *a* and *b*).



The pK_a values (Table 3) show that the *N*-hydroxy- and *N*-benzyloxy-amides are acids of almost equal strength (pK_a *ca.* 10) but, with the exception of α-dodecyl-*N*-hydroxyglutarimide, the *N*-hydroxy-imides are much more strongly acidic (pK_a *ca.* 7); this also may be due to equilibrium with the hydroxy-*N*-oxide form. Of the two pK_a values of (I), the ionisation (pK_a 5·05) is evidently due to the phenolic-type hydroxyl group since the corresponding *N*-benzyloxy- (XII, *a* or *b*) and *N*-methyl compounds are similar; the *N*-hydroxy-group of (I; R = R′ = Me) is therefore only weakly acidic (pK_a 10·35) and of about the same strength as the aliphatic hydroxamic acids. The alternative structure (XI) is improbable as it cannot account for the large difference between the two pK_a values; its exclusion is also supported by analogy with *N*-hydroxypyrid-2-one (Shaw, *loc. cit.*).

Note added, 18.1.55.—Kauffman and Burger (*J. Org. Chem.*, 1954, **19**, 1662) have recently described the synthesis of *N*-nitrosuccinimide and the catalytic hydrogenation of the latter to give succinimide (only 2·01 mols. of hydrogen being absorbed). This result provides a striking contrast with the resistance of the above *N*-hydroxyimides to hydrogenolysis.

Experimental

2 : 6-*Dimethoxy*-4-*methylpyridine* N-*Oxide*.—The dimethoxypyridine (8·5 g.) was treated with perbenzoic acid (25% excess) in chloroform at 0°, almost all the perbenzoic acid being consumed in 18 hr. The mixture was washed with sodium hydrogen carbonate solution and water, and distilled to give some starting material and an oil, b. p. 76—80°/1—1·5 mm., which partly crystallised. Trituration with light petroleum (b. p. 40—60°) and recrystallisation from the same solvent yielded fine needles of the N-*oxide* (0·45 g.), m. p. 68—69° (Found: C, 56·2; H, 6·2; N, 8·6. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·6; N, 8·3%).

The product (0·4 g.) was refluxed for 5 hr. with concentrated hydrochloric acid (10 c.c.), and the solution evaporated *in vacuo*; the only crystalline material isolated from the residual tar was ammonium chloride, evidently formed by decomposition.

2 : 6-*Dibromo*-4-*methylpyridine*.—Phosphorus tribromide (20 g.) was added to 2 : 6-dihydroxy-4-methylpyridine (6·0 g.), and the mixture heated (bath, 190—200°) for 7 hr. After cooling, the mass was poured into ice-water and steam-distilled, the crystalline dibromide (4·5 g.), m. p. 76·5—77·5°, being obtained from the distillate; ether-extraction of the distillate furnished more product (0·7 g.; total yield, 43%), m. p. 76—77°. Recrystallisation from water gave the pure dibromide, m. p. 87—79° (Bernstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1151, give m. p. 74—75°).

2 : 6-*Dibenzyloxy*-4-*methylpyridine*.—Potassium hydroxide (20 g.) was dissolved in benzyl alcohol (100 c.c.) at 150° and, after addition of xylene (35 c.c.), water was removed azeotropically by use of a Dean and Stark separator. The foregoing dibromide (16·2 g.) was added gradually, and the mixture refluxed (bath, 200—210°) for 1 hr. Addition of water, followed by ether-extraction and removal of solvents and benzyl alcohol *in vacuo*, yielded an oil which soon solidified. Recrystallisation from methanol furnished 2 : 6-*dibenzyloxy*-4-*methylpyridine* (14·6 g.)

which separated in clusters of prismatic needles, m. p. 55·5—56° (Found: C, 78·5; H, 6·3; N, 4·4. $C_{20}H_{19}O_2N$ requires C, 78·7; H, 6·3; N, 4·6%).

The amine (1·5 g.) in ethanol (100 c.c.) was hydrogenated by means of 5% palladised strontium carbonate catalyst (0·5 g.); absorption ceased when 2 mols. had been taken up. Evaporation of the filtered solution gave 2 : 6-dihydroxy-4-methylpyridine (0·55 g.), m. p. and mixed m. p. 192—194°.

α : β : N-*Trimethylglutaconimide*.—αβ-Dimethylglutaconic acid (15·7 g.) and methylamine in ethanol (60 c.c.; 35%) were heated slowly to 160°, then rapidly to 220°, and finally heated with a free flame until the product began to distil. Vacuum-distillation gave a brown viscous oil (10 g.), b. p. 95—110°/1 mm., which soon crystallised. Repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) containing a little acetic acid afforded the *imide* (2·8 g.), colourless plates, m. p. 91·5—92·5° (Found: C, 62·2; H, 6·9. $C_6H_{11}O_2N$ requires C, 62·7; H, 7·2%).

N-*Benzyloxy-αβ-dimethylglutaconimide*.—A mixture of αβ-dimethylglutaconic acid (1·0 g.), benzyloxyamine (Behrend and Leuchs, *Annalen*, 1890, **257**, 206) (0·8 g.), and xylene (10 c.c.) was refluxed for 45 min., water being removed by means of a reflux-head. On cooling, crystals, m. p. 124—125° (1·1 g.), separated; recrystallisation from xylene furnished the *benzyloxy-compound* in plates, m. p. 126—127° (Found: C, 68·6; H, 6·2; N, 5·9. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·2; N, 5·7%).

1 : 6(*or* 1 : 2)-*Dihydroxy*-3 : 4-*dimethylpyrid*-2(*or* 6)-*one*.—The foregoing benzyloxy-compound (13·5 g.) was suspended in ethanol (250 c.c.) and hydrogenated in the presence of 5% palladised strontium carbonate (1 g.) until absorption ceased (1·05 mols. taken up). After the mixture had been filtered at the b. p., the solution was concentrated and, on cooling, the crude product (6·5 g.), m. p. 155—157°, crystallised. The *hydroxamic acid* separated from methanol in plates, m. p. 157—158° (Found: C, 54·0; H, 5·8; N, 9·1. $C_7H_9O_3N$ requires C, 54·2; H, 5·9; N, 9·0%)

N-*Benzyloxysuccinamic Acid*.—Benzyloxyamine (6·3 g.) in benzene (20 c.c.) was added to a boiling solution of succinic anhydride (5·0 g.) in benzene (100 c.c.); the mixture was immediately cooled, and the resulting precipitate recrystallised from benzene–ethyl methyl ketone to give thin plates of the *acid* (7·6 g.), m. p. 95—96° (Found: C, 59·6; H, 5·7; N, 6·0%; equiv., 219. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%; equiv., 223).

Similarly (but using the anhydride in cold benzene) were prepared N-*benzyloxyglutaramic*, plates (92% yield) (from benzene–chloroform), m. p. 85—85·5° (Found: C, 60·5; H, 6·2; N, 6·0. $C_{12}H_{15}ON$ requires C, 60·7; H, 6·5; N, 5·9%), and N-*benzyloxymaleinamic acid*, rods (95% yield) [from ethyl methyl ketone–light petroleum (b. p. 60—80°)], m. p. 121—122° (Found: C, 59·7; H, 4·9; N, 6·1. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

N-*Hydroxysuccinamic Acid*.—The benzyloxy-acid (4·3 g.) in ethyl methyl ketone was hydrogenated as above, yielding the acid (1·45 g.), which separated from ethyl methyl ketone in prisms, m. p. 105—106° (Found: C, 36·5; H, 5·6; N, 10·0. Calc. for $C_4H_7O_4N$: C, 36·1; H, 5·3; N, 10·5%). Errara (*Gazzetta*, 1895, **25**, II, 25) described the preparation of this *compound* from succinic anhydride and hydroxylamine in ethanol but did not report the m. p.

N-*Hydroxyglutaramic acid* (77% yield), obtained similarly, formed prismatic needles, m. p. 122—124°, from ethyl methyl ketone (Found: C, 41·0; H, 6·2; N, 9·7. $C_5H_9O_4N$ requires C, 40·8; H, 6·2; N, 9·5%).

N-*Benzyloxysuccinimide*.—Succinic anhydride (0·8 g.) and benzyloxyamine (1·0 g.) were heated for 30 min. (bath, 180°). On cooling, the mass solidified and recrystallisation from benzene yielded the *imide* (1·25 g.) as prismatic needles, m. p. 140—141° (Found: C, 64·5; H, 5·3; N, 6·7. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%).

The following were prepared similarly: N-*Benzyloxyglutarimide* (44%), prismatic needles (from ether–chloroform), m. p. 140—141° (Found: C, 65·3; H, 5·9; N, 6·3. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4%). N-*Benzyloxy-α-dodecylglutarimide* (60%), needles [from light petroleum (b. p. 60—80°)], m. p. 69—70° (Found: C, 74·3; H, 9·8; N, 3·7. $C_{24}H_{37}O_3N$ requires C, 74·4; H, 9·6; N, 3·6%). N-*Benzyloxy-αβ-dimethylmaleinimide* (76%), plates, m. p. 87·5—89°, from light petroleum (b. p. 60—80°) (Found: C, 67·8; H, 5·5; N, 6·0. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

N-*Hydroxysuccinimide*.—Hydrogenation of the benzyloxyimide (5 g.) in ethyl methyl ketone (60 c.c.; dried over K_2CO_3) was carried out as in the previous example. The product crystallised from xylene–ethyl methyl ketone in plates, m. p. 94—95° (Found: C, 42·0; H, 4·4; N, 12·1. Calc. for $C_4H_5O_3N$: C, 41·7; H, 4·4; N, 12·2%). Dried solvents were used for the hydrogenation and recrystallisation since the substance is decomposed by warm water. [Errara (*loc. cit.*) probably obtained the same product by dehydration of *N*-hydroxysuccinamic

acid with sulphuric acid but did not give the m. p. Groth ("Chemische Krystallographie," 1910, **3**, 272) described the crystalline form and reported m. p. *ca.* 87° but gave no experimental details.] Treatment with acetic anhydride gave the acetyl derivative, m. p. **131—132°**; Hurd, Buess, and Bauer (*J. Org. Chem.*, **1954**, **19**, 1140) give m. p. 131°.

In the same manner were prepared *N-hydroxyglutarimide* (83%), fine needles, m. p. 108—109°, from xylene–ethyl methyl ketone (Found: C, 47·1; H, 5·6; N, 10·9. $C_5H_7O_3N$ requires C, 46·6; H, 5·5; N, 10·9%), and *α-dodecyl-N-hydroxyglutarimide* (95%), needles, m. p. 89—90°, from light petroleum (b. p. 60—80°) (Found: C, 69·0; H, 10·4; N, 4·9. $C_{17}H_{31}O_3N$ requires C, 68·6; H, 10·5; N, 4·7%).

N-Hydroxy-αβ-dimethylmaleinimide.—5% Palladised strontium carbonate (0·5 g.) was reduced with hydrogen, and the benzyloxy-imide (2·0 g.) was then added. Absorption almost ceased when 1 mol. of hydrogen had been taken up; evaporation of the filtered solution and crystallisation of the residue from benzene furnished *N-hydroxy-αβ-dimethylmaleinimide* (0·45 g.), plates, m. p. **126—127°** (Found: C, 51·3; H, 5·1; N, 9·8. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

N-Hydroxy-meso-*αβ-dimethylsuccinimide.*—*N*-Benzyloxy-αβ-dimethylmaleinimide (7·0 g.) was hydrogenated in the presence of palladium oxide on strontium carbonate (1·0 g.; 5% of Pd); 2 mols. of hydrogen were rapidly absorbed. Isolated in the usual manner, the *imide* separated from ethyl methyl ketone–light petroleum (b. p. 60—80°) in rectangular plates, m. p. 71—72° (Found: C, 47·2; H, 6·3; N, 9·5. $C_6H_9O_3N,\frac{1}{2}H_2O$ requires C, 47·4; H, 6·6; N, 9·2%). The substance was hygroscopic; the analytical sample was dried at room temperature in a high vacuum.

α : β : N-*Trimethylmaleinimide.*—Xylene (25 c.c.) and methylamine in ethanol (1 c.c.; 32%) were added to αβ-dimethylmaleic anhydride (1·0 g.) dissolved in benzene (5·5 c.c.), and the mixture was refluxed until no more aqueous phase could be collected. Concentration to *ca.* 10 c.c., followed by vacuum-distillation, gave the *imide* (0·6 g.), b. p. 130—133°/60 mm., n_D^{20} 1·4896 (Found: C, 60·4; H, 6·7. $C_7H_9O_2N$ requires C, 60·4; H, 6·5%).

NN'-*Dibenzyloxy-α-dodecylglutaramide.*—α-Dodecylglutaric anhydride (10 g.) and benzyloxyamine (4·3 g.) were refluxed with xylene (50 c.c.) for 30 min. Evaporation under reduced pressure and repeated recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) furnished the *diamide* (3·4 g.), plates, m. p. 113—114° (Found: C, 72·8; H, 9·2; N, 5·6. $C_{31}H_{46}O_4N_2$ requires C, 72·9; H, 9·1; N, 5·5%).

N-Benzyloxymaleinimide.—A suspension of *N*-benzyloxymaleinamic acid (13 g.) in benzene (300 c.c.) was refluxed for 2·5 hr. with thionyl chloride (26 c.c.). The solution was stirred at 5—10° while pyridine (26 c.c.) was slowly added, and then for another 15 min. After addition of water (500 c.c.), the separated aqueous layer was extracted with ether; the combined organic layers were washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation and crystallisation from light petroleum (b. p. 60—80°) yielded the *imide* (9·1 g.), needles, m. p. 80—81° (Found: C, 65·4; H, 4·6; N, 6·7. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5; N, 6·9%).

NN-*Diacetyl*-O-*benzylhydroxylamine.*—*N*-Benzyloxymaleinamic acid (5 g.) was heated with acetic anhydride (50 c.c.) at 150° (b. p.) for 5 min. Evaporation *in vacuo* and crystallisation from light petroleum (b. p. 60—80°) afforded needles of the *imide* (3·35 g.), m. p. 101—102° (Found: C, 63·9; H, 6·1; N, 6·3; Ac, 43·6. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3; N, 6·8; Ac, 41·5%). The same product, m. p. and mixed m. p., was obtained directly from benzyloxyamine and acetic anhydride in the same manner.

NN-*Diacetylhydroxylamine.*—Catalytic hydrogenation of the foregoing benzyloxy-compound yielded the *hydroxy-imide*, needles, m. p. 88—88·5°, from benzene–light petroleum (b. p. 60—80°). On admixture with *ON*-diacetylhydroxylamine (Hantzsch, *Ber.*, **1892**, **25**, 701), the m. p. was depressed to 63—67° (Found: C, 40·9; H, 5·9; N, 11·7. $C_4H_7O_3N$ requires C, 41·0; H, 6·0; N, 12·0%).

The authors are grateful to Dr. R. E. Bowman for valuable advice and suggestions, and to Dr. J. M. Vandenbelt and Mr. R. B. Scott (Parke, Davis and Company, Detroit) and to Miss E. M. Tanner for the spectroscopic measurements and potentiometric titrations and for helpful advice on their interpretation.

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The Configuration at $C_{(25)}$ in the Natural Spirostan Sapogenins.

By V. H. T. James.

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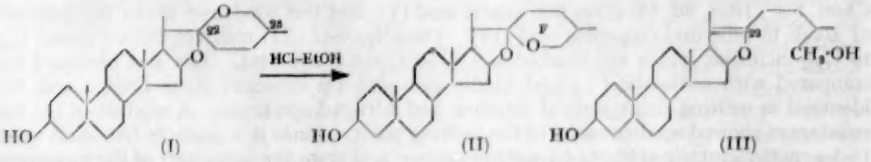
*pseudo*Hecogenin and *pseudo*diosgenin have been degraded to (−)-α-methylglutaric acid, which contains the original asymmetric carbon atom $C_{(25)}$. (−)-α-Methylglutaric acid has been configuratively related to (+)-methylsuccinic acid and so to glyceraldehyde.

The difference between the isomeric sapogenins sarsasapogenin and smilagenin was originally shown to be confined to the side chain by Farmer and Kon (*J.*, 1937, 414), and these authors considered it to be one of configuration of the asymmetric carbon atom in the terminal ring. Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1939, **61**, 846) proposed the spiroketal formulation (I) for sarsasapogenin, and (II) for an isomeric transformation product, later accepted as being identical with smilagenin.



(I) (II) (III)

The instability of sarsasapogenin to ethanolic hydrochloric acid was interpreted as an opening of the terminal oxide ring, with subsequent reclosure in the opposite direction to give smilagenin. Marker and Rohrman (*ibid.*, 1940, **62**, 518) also found that treatment of a sapogenin with acid anhydrides converted it into an isomer, designated the *pseudo*-sapogenin and formulated as (III). The reported observation that *pseudo*sarsasapogenin and *pseudo*smilagenin were identical further supported the spiroketal formulation, since the asymmetry at $C_{(22)}$ would be lost when ring F opens.

On the basis of experiments inter-relating various sapogenins, and their stability towards ethanolic hydrochloric acid, Marker and his co-workers established the existence of two series of compounds: (*a*) the "normal" sapogenins, substituted at various carbon atoms in the steroid nucleus, but having the same side chain as sarsasapogenin, and (*b*) their corresponding isomers, differing only at $C_{(22)}$, the "*iso*"-sapogenins.

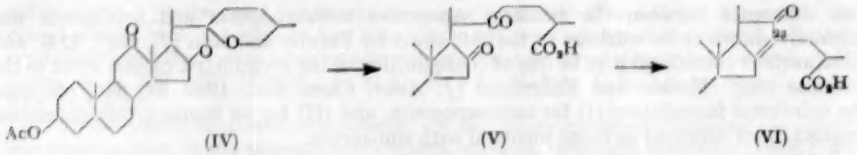
The other asymmetric centre in ring F, $C_{(25)}$, was neglected, and the present work was undertaken in order to ascertain the configuration of this carbon atom. However whilst this was in progress, Scheer, Kostic, and Mosettig (*ibid.*, 1953, **75**, 4871) reported that, by preparing derivatives of *pseudo*sarsasapogenin and *pseudo*smilagenin, they had established a difference between these compounds. They also found that on oxidation these *pseudo*-compounds gave respectively (+)- and (−)-α-methylglutaric acid.

Experimental work in this laboratory involved the degradation of the sapogenins diosgenin and hecogenin, both members of the "*iso*"-series. By isomerisation to the corresponding *pseudo*-compound, followed by oxidation, hecogenin yielded a neutral fraction, *allo*pregn-16-ene-3 : 12 : 20-trione, and an acidic fraction containing carbon atoms $C_{(22)}$ to $C_{(27)}$ inclusive as (−)-α-methylglutaric acid. Diosgenin similarly treated also gave the lævorotatory α-methylglutaric acid. Hence with respect to configuration at $C_{(25)}$, the three "*iso*"-sapogenins, smilagenin, diosgenin, and hecogenin, all belong to one series, whilst sarsasapogenin and *neo*tigogenin (Callow and James, *Chem. and Ind.*, 1954, 691) belong to the other.

The knowledge of the direction of the optical rotation of the α-methylglutaric acid which can be derived from a sapogenin does not enable an absolute assignment of configuration to be made to ring F, since the configurations of the α-methylglutaric acids are not known with certainty. The configuration of methylsuccinic acid has been determined by Fredga and Leskinen ("The Svedberg, 1884 $\frac{30}{8}$ 1944," Almquist and Wiksells, Uppsala, 1944, p. 261;

Arkiv Kemi, Min., Geol., 1944, **19**, *B*, No. 1) and Freudenberg and Hohmann (*Annalen*, 1953, **584**, 54); further, Fredga (*ibid.*, 1947, **24**, *A*, No. 32) has obtained an indication by the method of quasiracemic compounds that (+)-methylsuccinic acid and (−)-α-methylglutaric acid are configuratively related. Fredga points out, however, that a more direct means of obtaining this correlation would be desirable.

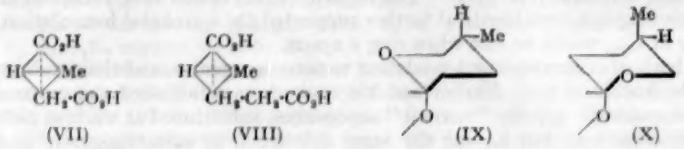
The obvious methods of inter-relating the two homologous acids, *i.e.*, by one-carbon degradation of α-methylglutaric acid, or by synthesis from methylsuccinic acid meet difficulties, and experiments in this direction were not successful. However, oxidation of hecogenin acetate (IV) directly with chromic oxide (cf. Fieser and Jacobsen, *J. Amer.*



(IV) (V) (VI)

Chem. Soc., 1938, **60**, 28) gives hecogenoic acid (V), and this condenses under the influence of alkali to anhydrohecogenoic acid (VI). Ozonolysis of (VI) removes carbon atoms $C_{(23)}$ to $C_{(27)}$ inclusive, which are isolated as (+)-methylsuccinic acid. The acid obtained was compared with authentic (+)-acid kindly provided by Professor Arne Fredga and was identical in melting point, optical rotation, and infra-red spectrum. A mixture of the two substances showed no depression of the melting point. Since it is possible to obtain either (−)-α-methylglutaric acid or (+)-methylsuccinic acid from the same part of the sapogenin, these two acids are obviously related stereochemically, and the conclusion reached by Fredga using physical methods is unambiguously confirmed.

The configuration of (+)-methylsuccinic acid is represented by (VII), so (−)-α-methylglutaric acid is (VIII). If it is assumed that ring F of the sapogenins is in the "chair"



(VII) (VIII) (IX) (X)

conformation in a position which appears to be comparatively unhindered, the terminal rings of hecogenin, diosgenin, and smilagenin will be shown by either (IX) or (X), according to the configuration assigned to $C_{(22)}$.

Experimental

Infra-red absorption spectra were determined on a Perkin–Elmer double-beam instrument by Miss Patricia Dodson.

Oxidation of pseudo*Sapogenins*.—The *pseudo*-compound was prepared by heating the sapogenin at 200° with acetic anhydride for 5 hr. in a sealed tube, followed by removal of excess of anhydride, hydrolysis, and crystallisation from acetone.

*pseudo*Hecogenin (2·0 g.) was dissolved in glacial acetic acid (100 ml.) and to this solution at room temperature was added a solution of chromium trioxide (2·5 g.) in 25 ml. of aqueous acetic acid (80%). The temperature rose to 24° and the solution was set aside for 1 hr. before dilution with water. The product was extracted with ether (5 times), and the ether was washed once with water, dried, and evaporated. The non-crystalline residue was warmed with 20 ml. of N-sodium hydroxide on a steam-bath for 15 min. and then diluted to 300 ml. with water. Extraction (4 times) with ether removed non-acidic material (A), and the aqueous layer was then acidified with dilute hydrochloric acid and ether-extracted (5 times). The ether was dried and evaporated, to yield a brown gum (1 g.). This was chromatographed on a partition column containing "Celite" (100 g.) made up in chloroform equilibrated with 0·5N-sulphuric acid. Some brown material which ran with the solvent front was eluted with equilibrated chloroform, and then elution with chloroform containing 2·5% of *n*-butanol gave the only other acidic

fraction obtained. Extraction of this material with aqueous sodium hydrogen carbonate, followed by acidification and ether-extraction, gave α-methylglutaric acid. Crystallised twice from ether–pentane, the acid (80 mg.) had m. p. 78·5—83°, $[\alpha]_D^{22}$ −17° (in EtOH) (Found: C, 49·8; H, 7·2. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·9%). The infra-red spectrum is given in C.S. no. 167.*

Similar treatment of *pseudo*diosgenin gave α-methylglutaric acid, m. p. 82—84°, $[\alpha]_D^{23}$ −21° (in EtOH).

The ether solution of the material (A) was washed with water, dried, and evaporated, to give white crystals (600 mg.). These were chromatographed on alumina (Savory and Moore) and 1 : 4 ether–benzene eluted solid, which crystallised from benzene–light petroleum (b. p. 60—80°) as needles of allo*pregn*-16-*ene*-3 : 12 : 20-*trione*, m. p. 225—230°, $[\alpha]_D^{20}$ +124° (in MeOH), $\lambda_{max.}$ (in MeOH) 227—228 mμ (log ε 3·9) (Found: C, 76·7; H, 8·5. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%). The infra-red spectrum (C.S. no. 168) of this compound in compressed potassium bromide showed bands at 1711 (ketone) and 1675 and 1596 cm.$^{-1}$ (αβ-unsaturated ketone).

Hecogenoic Acid.—To hecogenin acetate (20 g.) in glacial acetic acid (distilled from chromic oxide, 400 ml.), kept at 60—65°, was added during 4 hr., with constant stirring, a solution of chromic oxide (12 g.) in 80% aqueous acetic acid (200 ml.). After a further 1 hr., the solution was set aside overnight. Ethanol (5 ml.) was added and the solution was concentrated at reduced pressure and diluted with water, then extracted with ether. After being washed with water, the ether was extracted with 3% sodium hydroxide solution, and the alkali extract washed with ether; warming the alkali solution on the steam-bath for 15 min., followed by acidification with dilute sulphuric acid, precipitated solid. This was collected (4·17 g.); crystallised from aqueous acetone it gave *hecogenoic acid* as hexagonal plates, m. p. 242·5—244·5°, $[\alpha]_D^{22}$ −73° (in $CHCl_3$) (Found: C, 70·6; H, 8·8. $C_{27}H_{40}O_6$ requires C, 70·4; H, 8·8%). The infra-red absorption spectrum (C.S. no. 169) of the compound in compressed potassium bromide showed strong bands at 3300, 1738, 1713, and 1692 cm.$^{-1}$.

Anhydrohecogenoic Acid.—Hecogenoic acid (5 g.), dissolved in ethanol (50 ml.) and water (20 ml.), was treated with sodium hydroxide (2 g.). After refluxing for 1 hr., the solution was diluted with water (50 ml.) and acidified with dilute sulphuric acid. The precipitated solid was collected and dried (4·4 g.). Trituration with ether and filtration, followed by crystallisation from chloroform–acetone, gave *anhydrohecogenoic acid* as needles, m. p. 278—280°, $[\alpha]_D^{19}$ −30° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 242—243 mμ (Found: C, 73·1; H, 8·5. $C_{27}H_{38}O_5$ requires C, 73·3; H, 8·7%). The infra-red absorption spectrum (C.S. no. 170) of the compound as a Nujol mull showed strong bands at 3290, 1724, 1703, 1693, and 1657 cm.$^{-1}$.

Ozonolysis. Anhydrohecogenoic acid (1·0 g.) in chloroform (500 ml.), cooled in alcohol–carbon dioxide, was ozonised for 2 hr. The solution, then blue, was distilled, to give a residual gum. This was heated on the steam-bath with water (10 ml.) and 30% hydrogen peroxide (10 ml.) for 15 min. The material was then extracted with ether, and the ether extracted with 2N-sodium hydroxide. Acidification, ether-extraction, drying, and evaporation yielded 1·0 g. of brown gum. Of this, 800 mg. were chromatographed on "Celite" as for the α-methylglutaric acid. Two fractions were obtained: the more polar, eluted with chloroform containing 10% of *n*-butanol and crystallised from benzene, gave (+)-methylsuccinic acid (41·2 mg.), m. p. 114—115°, $[\alpha]_D^{23}$ +10° (in H_2O) (Found: C, 45·4; H, 6·4. Calc. for $C_5H_8O_4$: C, 45·4; H, 6·1%). The infra-red absorption spectrum (C.S. no. 171) of the acid was identical with that (C.S. no. 172) of an authentic specimen of (+)-methylsuccinic acid, and the two samples showed no depression of m. p. on admixture.

For both methylsuccinic and α-methylglutaric acid, the spectra of the optically active isomers differed from those (C.S. nos. 173 and 174 respectively) of the racemic (±)-acids in minor points.

The author is indebted to Dr. D. A. H. Taylor for suggesting the problem, and to Dr. R. K. Callow for advice and encouragement.

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Mill Hill, London, N.W.7. [*Received, October 26th*, 1954.]

* Spectra thus designated have been deposited with the Chemical Society. Copies price 3*s.* 0*d.* per copy per spectrum, may be obtained on application, quoting the C.S. no., from the General Secretary.

Some Aspects of the Oxidation of Di- and Tri-phenylmethane.

By D. D. K. Grant and C. F. H. Tipper.

[Reprint Order No. 5698.]

Certain previous unusual results in the reaction of liquid diphenylmethane with oxygen are shown to be due to impurities. The purified hydrocarbon is oxidized, under various conditions, at rates which can be explained by a normal autoxidation mechanism involving hydroperoxides and a succession of free radicals, and the presence of such radicals was proved. The addition of organic acids markedly altered the form of the curves of oxygen-uptake and hydroperoxide yield, owing to catalysis of the ionic decomposition of the hydroperoxide. Some acids appear in addition to increase the rate of formation of the hydroperoxide.

The oxidation of triphenylmethane is complicated even in its initial stages.

The reactions of the phenylmethanes with molecular oxygen in the liquid phase show a number of peculiarities. Waters (*J.*, 1946, 1151) found that the oxidation of triphenylmethane catalyzed by chromic anhydride at 20—45° is slower than that of diphenylmethane, although it might be expected that the methane hydrogen atom in the former would be easily removable. Also water inhibits the oxidation of tri- but not of di-phenylmethane (Stevens and Roduta, *J. Amer. Chem. Soc.*, 1935, **57**, 2380). Larsen, Thorpe, and Anfield (*Ind. Eng. Chem.*, 1942, **34**, 282) state that the uptake of oxygen by diphenylmethane at 110° stops completely after 500 ml./mole have been absorbed, and that the products are benzaldehyde plus residual inhibitors, in contrast to Stevens and Roduta (*loc. cit.*) who report only benzophenone as a product.

Because of the unusual results obtained by Larsen, Thorpe, and Anfield (*loc. cit.*), the oxygen-uptake characteristics of various specimens of diphenylmethane were studied at 105°. Typical curves are shown in Fig. 1. The rate of absorption accelerated from zero to a maximum, which occurred after ~0·02 mole of oxygen per mole of hydrocarbon had been taken up. This acceleration period was shortened or eliminated by not removing any " peroxide " initially present (due to exposure to air, sunlight, etc.), but the maximum rate was not affected: this was demonstrated by removal of peroxide, preferably by chromatography. With commercial diphenylmethane, purified by recrystallization or vacuum- or steam-distillation, or with specimens synthesized in various ways, oxygen-uptake ceased quite sharply after between 250 and 2000 ml. per mole of hydrocarbon had been absorbed (Fig. 1, *a* and *b*). The gas above the solution was still practically all oxygen, but the mixture had become dark brown and, as judged by smell, phenol and benzaldehyde were present. The hydroperoxide yield fell off rapidly from nearly 100%, just before the cessation of oxidation. However, when the diphenylmethane was purified by shaking it six times with concentrated sulphuric acid, washing it with water, drying it, and chromatography under nitrogen, the oxygen-uptake and hydroperoxide-yield curves (Fig. 1, *c*) resembled those for the oxidation of other hydrocarbons in the liquid phase. When the oxidation rate fell off from the maximum (0·75 ± 0·04 ml. at N.T.P. per g. of diphenylmethane per hour) the solution again became brown and smelt of phenol and benzaldehyde. It seems that diphenylmethane as normally obtained or prepared contained an impurity, not removed by physical methods, and possibly anthracene (Orndorff, Gibbs, McNulty, and Shapiro, *J. Amer. Chem. Soc.*, 1927, **49**, 1541), which catalyzed the decomposition of the hydroperoxide, when this reached a critical concentration, producing a powerful inhibitor which prevented further oxygen-uptake. It is significant that, according to the literature, diphenylmethane has usually been purified for physical or chemical measurements by distillation or crystallization.

The oxygen-uptake characteristics of liquid triphenylmethane at 105° were studied, in order to compare them with those of diphenylmethane, and to see whether sudden cessation of the reaction occurred. Commercial triphenylmethane gave oxygen-uptake curves similar to those of the final specimen of diphenylmethane (Fig. 1*c*). The maximum rate

(about 0·53 ml. at N.T.P. per g. per hr.) occurred after approximately 0·01 mole of oxygen has been absorbed per mole of hydrocarbon, and the rate fell off again after about 0·04 mole per mole had been taken up. However, the " hydroperoxide " yield was always less than 60%, and fell off to zero after 0·10—0·15 mole of oxygen per mole of hydrocarbon had been absorbed, although the liquid was still taking up gas at 25—40% of the maximum rate. The products then were a dark brown crystalline solid and a red liquid condensate in the neck of the reaction flask. There was a phenolic and sometimes a sweet-scented smell. Stevens and Roduta (*loc. cit.*) found that benzophenone and phenol were produced during the oxidation of triphenylmethane. There was an indication that different methods of

FIG. 1.

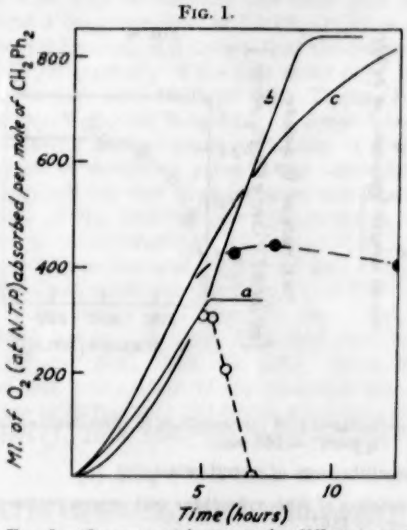

FIG. 2.

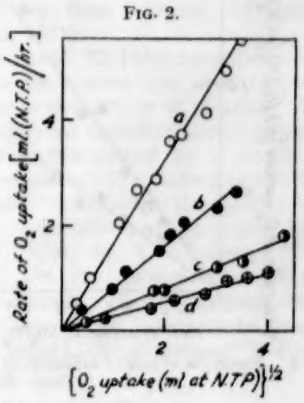

FIG. 1. *Oxygen-uptake curves for different samples of diphenylmethane. Temp.* = 105° O_2 *press.* = 760 *mm.*

a, CH_2Ph_2 *purified by vac. distn. and chromatographed under* N_2: —○—, *oxygen as hydroperoxide. b*, CH_2Ph_2 *prepared by reaction of* C_6H_6, $C_6H_5{\cdot}CH_2{\cdot}OH$, AcOH, *and conc.* H_2SO_4 *c*, CH_2Ph_2 *purified by treatment with conc.* H_2SO_4, *etc.* (*ordinates* × 5, *abscissæ* × 4). —●—, *oxygen as hydroperoxide.*

FIG. 2. *Variation of rate of oxidation of diphenylmethane with amount of reaction during period of acceleration.*

a, 3 *g. of* CH_2Ph_2 *at* 115°, *and* 760 *mm. of* O_2.
b, 3 ,, ,, 105°, ,, ,, ,,
c, 2 ,, ,, 115°, ,, 67 ,, (*abscissæ* × 0·5).
d, 3 ,, ,, +6·7 *g. of* PhCl *at* 115°, *and* 760 *mm. of* O_2 (*abscissæ* × 0·5).

peroxide determination gave somewhat different values of titratable oxygen at the same stage in the reaction, and possibly the products included some bistriphenylmethyl peroxide, unless these methods were not accurate for triphenylmethyl hydroperoxide. The oxidation even in the initial stages seems to be more complicated than that of diphenylmethane and was not studied further.

The reaction of " pure " diphenylmethane (*i.e.*, the hydrocarbon after treatment with concentrated sulphuric acid, etc.) with oxygen seems to follow the same course as those of olefin oxidations in solution (Bolland, *Quart. Reviews*, 1949, **3**, 1), in so far as the hydroperoxide is formed quantitatively at first but breaks down slowly later to form the stable products. The kinetics of the initial stages of the oxidation of the " pure " material were therefore studied to provide a further comparison.

It was found that, during the acceleration period, the rate of oxygen uptake at any time was proportional to the square root of the oxygen absorbed up to that time (Fig. 2, *a* and *b*). The rate during this period is therefore proportional to $[CHPh_2{\cdot}O{\cdot}OH]^{\frac{1}{2}}$, the

hydrocarbon concentration being virtually constant. However, as can be seen from Fig. 1, the maximum rate was virtually independent of hydroperoxide concentration. Dilution of the diphenylmethane with chlorobenzene, an inert solvent, did not alter the square-root dependence of the rate during the acceleration period on hydroperoxide concentration (*e.g.*, Fig. 2*d*). Both the slope of this line and the maximum rate are proportional to the mole fraction of hydrocarbon at 115° (Fig. 3). A few experiments seemed to show that at 105° the dependence of the maximum rate on the concentration of diphenylmethane was about 1·5 rather than 1·0. The yield of hydroperoxide was again practically quantitative

FIG. 3.

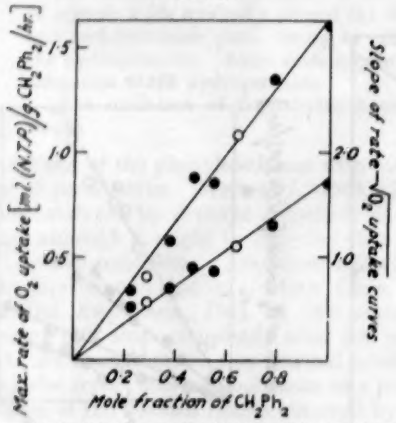

FIG. 4.

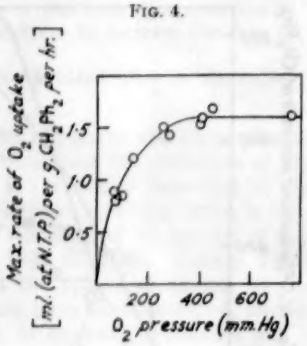

FIG. 3. *Variation of rate of oxidation of diphenylmethane with concentration in chlorobenzene solution. Temp.* = 115°. O_2 *press.* = 760 *mm.*

Points marked ● *represent the mean of several values.*

FIG. 4. *Variation of maximum rate of oxidation of diphenylmethane with oxygen pressure. Temp.* = 115°.

until the rate commenced to decrease from its maximum value. Above about 300 mm. the pressure of oxygen had little effect on the uptake curves, but below this value the rate began to fall off (Fig. 4). The plots for rate against (uptake)$^{\frac{1}{2}}$ remained linear as far as could be ascertained (*e.g.*, Fig. 2*c*), but the slope decreased in a manner parallel with the decrease in maximum rate.

The kinetics of the initial stages of the oxidation of diphenylmethane can be summarized in two equations: during the acceleration period,

$$\text{rate} = k[CHPh_2{\cdot}O{\cdot}OH]^{\frac{1}{2}} \,.\, [CH_2Ph_2][O_2]/(\alpha + [O_2])$$

and max. rate $= k'[CH_2Ph_2][O_2]/(\beta + [O_2])$ (in any case at 115°), where k, k', α, and β are constants.

The overall activation energies, calculated from the average slopes of the plots for rate against (uptake)$^{\frac{1}{2}}$ or from the average maximum rates at 105° and 115°, are the same within experimental error, *viz.*, 21·2 and 21·9 kcal./mole, respectively.

The first equation can readily be explained by postulating a reaction scheme, which is a special case of the general free-radical chain mechanism put forward by Bolland (*loc. cit.*), autocatalysis being due to the decomposition of a small proportion of the hydroperoxide formed:

(1) $CHPh_2{\cdot}O{\cdot}OH \longrightarrow$ radicals R· (first-order reaction)
(2) $R{\cdot} + CH_2Ph_2 \longrightarrow RH + Ph_2CH{\cdot}$
(3) $Ph_2CH{\cdot} + O_2 \longrightarrow CHPh_2{\cdot}O{\cdot}O{\cdot}$
(4) $CHPh_2{\cdot}O{\cdot}O{\cdot} + CH_2Ph_2 \longrightarrow CHPh_2{\cdot}O{\cdot}OH + Ph_2CH{\cdot}$
(5) $2CHPh_2{\cdot}O{\cdot}O{\cdot} \longrightarrow$ inert products (termination at " high " oxygen pressures)

Assuming that the chains are long, we have

$$-d[O_2]/dt = k_3[Ph_2CH\cdot][O_2] = k_4[CHPh_2\cdot O\cdot O\cdot][CH_2Ph_2]$$

Strictly, $[CHPh_2\cdot O\cdot O\cdot]$ is not constant, since the rate is increasing, but this increase is very slow compared with the rate of the radical reactions and so $d[CHPh_2\cdot O\cdot O\cdot]/dt$ can be taken as zero. Then at any time before the maximum rate is reached

$$-d[O_2]/dt = (k_1/k_5)^{\frac{1}{2}}k_4[CHPh_2\cdot OOH]^{\frac{1}{2}}[CH_2Ph_2]$$

The fall-off in the rate at " low " oxygen pressures would be due to reaction (3) becoming so slow that $Ph_2CH\cdot$ radicals can take part in termination reactions. Although the unimolecular decomposition of $CHPh_2\cdot O\cdot OH$ is postulated to obtain agreement with the experimental kinetics, it is known that the decomposition of hydroperoxides, unstable only above 100°, is generally of the first order (*e.g.*, Bell, Raley, Rust, Senbold, and Vaughan, *Discuss. Faraday Soc.*, 1951, **10**, 242; Tipper, *J.*, 1953, 1675).

Tobolsky, Metz, and Mesrobian (*J. Amer. Chem. Soc.*, 1950, **72**, 1942) have shown that a straightforward mathematical extension of Bolland's mechanism can account for the phenomenon of maximum rates in the autoxidation of hydrocarbons in solution. However, they predicted that the maximum rate of an uncatalyzed oxidation should depend on the square of the hydrocarbon concentration and be accompanied by a steady concentration of hydroperoxide. This was not so in the present work, a feature of which was that the uptake (in moles of oxygen per mole of diphenylmethane) before the maximum rate was reached was small compared with that during the autoxidations of many other hydrocarbons (*e.g.*, Bolam and Sim, *J. Soc. Chem. Ind.*, 1941, **60**, 51; Larsen, Thorpe, and Anfield, *loc. cit.*; Bolland, *Proc. Roy. Soc.*, 1946, *A*, **186**, 218; Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201). Since the maximum rate of diphenylmethane oxidation was independent of the concentration of hydroperoxide, this must be involved in both the initiation and the termination step at this stage in the oxidation. Robertson and Waters (*J.*, 1948, 1585) have suggested the reaction

$$(6)\ RO_2 + OH \text{ (from the hydroperoxide)} \longrightarrow ROH + O_2$$

to account for the levelling-off in the rate during the autoxidation of tetralin. This requires that the maximum rate be again proportional to the square of the hydrocarbon concentration, however. Possibly traces of a retarder were being formed by a very small amount of hydroperoxide decomposition, and the reaction

$$(7)\ CHPh_2\cdot O\cdot O\cdot + \text{retarder} \longrightarrow \text{inert products}$$

replaced reaction (5). If the concentration of retarder was proportional to the hydroperoxide concentration, the observed kinetics at 115° would be explained. The higher order with respect to the concentration of diphenylmethane at 105° may have been due to the occurrence of reaction (6) as well as (7). The decrease in the maximum rate at " low " oxygen pressures was again probably the result of $Ph_2CH\cdot$ radicals beginning to take part in termination reactions.

The presence of free radicals during the oxidation was confirmed by the addition of 8 mg. of β-naphthol, known to be an inhibitor of radical reactions, to 2 g. of diphenylmethane. This completely prevented oxygen uptake at 115° for at least 54 hr. Addition of 10 mg. of phenol to 2 g. of diphenylmethane caused the absorption of gas to be very slow for about 15 hr., after which the oxidation proceeded normally. The rôle of phenol in the autoxidation of diphenylmethane is difficult to assess, since it is probably formed in some quantity during the later stages of the reaction which is still proceeding at $\sim\frac{1}{3}$ to $\frac{1}{2}$ of the maximum rate. It can therefore scarcely be responsible for the sudden cessation of the oxidation of " impure " diphenylmethane, but it might have acted as the retarder in reaction (7). There appears, however, to be a difference between the effect of phenol added initially and that formed during the oxidation.

The decomposition of hydroperoxides is greatly affected by conditions, especially the presence of acids or bases, and therefore it would be expected that these substances would

have an effect on the course of the oxidation of a hydrocarbon in solution. There have been few investigations of the effect of the solvent on such an oxidation. Some patents record different products from the use of different solvents, and Bolam and Sim (*loc. cit.*) found that there was a marked difference in the oxidation characteristics of methyl linoleate in neutral and in acidic or basic solvents. Morrell and Davis (*J. Soc. Chem. Ind.*, 1936, **55**, 237) and Paquot (*Bull. Soc. chim.*, 1941, **8**, 695) have also noted the marked effect of acetic acid on autoxidations in solution.

In the presence of 70 moles % of acetic acid the oxidation of " pure " diphenylmethane was very slow (~0·05 ml./g./hr.) and the concentration of hydroperoxide was negligible. With 65 moles % of butyric acid added, at 115° or 105° the uptake of oxygen appeared

FIG. 5.

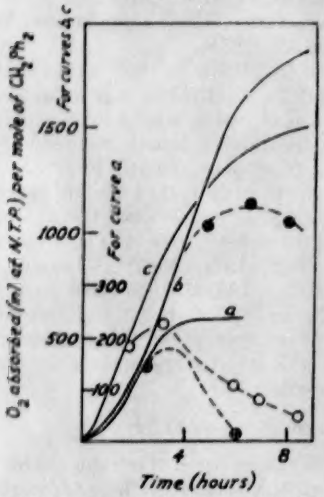

FIG. 6.

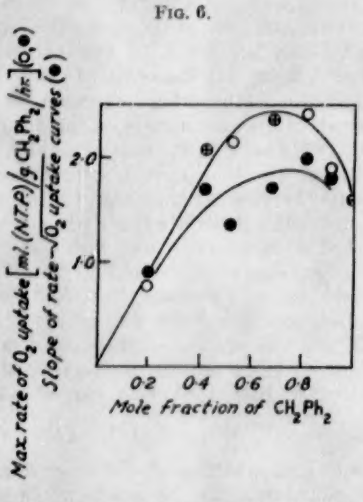

FIG. 5. *Oxygen-uptake curves for diphenylmethane in presence of some organic acids. Temp.* = 115°. O_2 *press.* = 760 *mm.*

a, CH_2Ph_2 + 65 *moles* % *of butyric acid.* —⊕—, *oxygen as hydroperoxide.*
b, CH_2Ph_2 + 58 *moles* % *of benzoic acid.* —●—, *oxygen as hydroperoxide.*
c, CH_2Ph_2 + 55 *moles* % *of phenylacetic acid.* —○—, *oxygen as hydroperoxide.*

FIG. 6. *Variation of rate of oxidation of diphenylmethane with concentration in the presence of benzoic acid. Temp.* = 115°. O_2 *press.* = 760 *mm.*

Points marked ⊕ *represent the mean of several values.*

to follow the same course as with the same concentration of chlorobenzene as diluent until there was a sudden reduction in the rate of absorption to a low value (<0·09 ml./g./hr.), and at the same time the yield of hydroperoxide which had been nearly quantitative dropped sharply (Fig. 5*a*). Addition of 1·4 moles % of trichloroacetic acid, a strong acid, to a 38 mole % solution of diphenylmethane in chlorobenzene caused practically complete inhibition at 116° (~0·05 ml. of O_2 absorbed/g./hr.) and no hydroperoxide was present. The lack of uptake was real, since the gas above the solution at the end of an experiment was still practically all oxygen. The acids were obviously catalyzing the hydroperoxide decomposition in such a way that no fresh chain centres were formed, presumably to give ions; with butyric acid this only occurred after a certain amount of hydroperoxide had accumulated. The autocatalysis by the hydroperoxide was cut out, and the very slow uptake may have been due to a chain reaction initiated by a direct reaction with a high activation energy between diphenylmethane and oxygen.

With benzoic acid or phenylacetic acid as diluent the results are somewhat different. With the former there was a short acceleration period to a maximum rate much greater

than that with the same concentration of chlorobenzene as diluent, but the rate began to decrease at a lower uptake. The yield of hydroperoxide, which was practically quantitative during the acceleration period, fell off, and the hydroperoxide concentration reached a maximum during the period of maximum rate (Fig. 5*b*). A plot of rate against (O_2 uptake)$^{\frac{1}{2}}$ was again a straight line through the origin up to the attainment of the maximum rate. The variation of the slope of this line and of the maximum rate with hydrocarbon concentration is shown in Fig. 6. There is a maximum in both curves at about 75 moles % of diphenylmethane. When more than about 40 moles % of phenylacetic acid were added, the rate of oxygen uptake accelerated very rapidly from zero to its maximum value, and this rate was again very much greater than with an inert diluent. The rate of absorption tailed off sharply and the hydroperoxide yield, which was nearly 100% at the beginning, fell rapidly to a low level (Fig. 5*c*). With progressively less acid an increasingly long acceleration period occurred and the tail-off was more gradual. Neither acid absorbed oxygen by itself. Two effects were probably competing when diphenylmethane was oxidized in the presence of these two acids. At the beginning of the reaction there was rapid chain transfer to give reactive solvent radicals, leading to an increased rate in the initial stages; but later, acid-catalyzed decomposition of the hydroperoxide became increasingly prominent. With phenylacetic acid presumably a hydrogen atom from the CH_2 group would be removed in the solvent-transfer reaction but, although benzoic acid has never been considered prone to attack by free radicals, it seems likely that in these circumstances $Ph{\cdot}CO{\cdot}O{\cdot}$ radicals were formed, since chlorobenzene was inert. From the results it appears that the order of increasing reactivity towards $CHPh_2{\cdot}O{\cdot}O{\cdot}$ radicals is $CH_2Ph_2 < Ph{\cdot}CO_2H \ll CH_2Ph{\cdot}CO_2H$. It is possible that the sudden cessation of oxygen-uptake with impure diphenylmethane was due to the formation of an acid. Waters and Wickham-Jones (*J.*, 1951, 812) found that the addition of benzoic or trichloroacetic acid to benzaldehyde eliminated autocatalysis by the perbenzoic acid formed.

It may be mentioned that initial addition of small amounts of mercury (~1 mole %) inhibited the autoxidation; and when it was added during the course of a normal reaction, complete cessation of oxygen uptake took place, and the hydroperoxide concentration dropped rapidly.

In conclusion it can be said that, while the oxidation of triphenylmethane is complicated even in its initial stages, that of diphenylmethane fits into the general pattern of autoxidations in solution. However, the results illustrate again the vital rôle of hydroperoxides, and their modes of formation and decomposition, in the liquid-phase oxidation of hydrocarbons.

Experimental

The uptake of oxygen was followed by means of a conventional constant-pressure apparatus. Up to four 25-ml. flasks at a time contained the hydrocarbon with or without additive. They were immersed in an oil thermostat, constant to $\pm 0{\cdot}1°$ during an experiment, and were shaken about 400 times per min. The rate of shaking, unless low (<100 per min.), had no effect on the uptake curves within the experimental error. The flasks were connected to constant-pressure gas burettes by capillary tubing and the smallest lengths of pressure tubing possible. They were cleaned before use by washing them successively with soap and water, boiling alcoholic potash (EtOH 90, H_2O 5, KOH 5 parts), concentrated nitric acid, water, concentrated nitric acid, distilled water, and "AnalaR" acetone, and dried by heating them in a stream of air. Pipettes, etc., were cleaned as above but not heated. The air in the apparatus was swept out by pure oxygen before an experiment.

The "peroxide" content was determined by the iodometric method of either Skellon and Wills (*Analyst*, 1948, **73**, 78) or Wagner, Smith, and Peters (*Ind. Eng. Chem. Anal.*, 1947, **19**, 976). Gas samples were removed from above the reaction mixture by connecting the flask to an evacuated tube, and analyzed in a Bone and Wheeler apparatus.

The methods of purification of diphenylmethane have been discussed. The hydrocarbon was synthesized by three methods: reduction of benzophenone by sodium and alcohol; condensation of benzene and benzyl chloride in presence of mercuric chloride and aluminium; condensation of benzene and benzyl alcohol by acetic and concentrated sulphuric acids [see Beilstein's "Handbuch," V (Syst. No. 479), p. 589]. The alumina used for chromatography

was B.D.H. special. Triphenylmethane was recrystallized twice from alcohol and stored in a continually evacuated desiccator for some hours before use. Chlorobenzene was distilled twice, kept under nitrogen, and chromatographed under nitrogen before use. " AnalaR " acetic acid was distilled with 1% " AnalaR " acetic anhydride. " AnalaR " trichloroacetic acid was used directly. Butyric acid was distilled in a nitrogen atmosphere. Benzoic acid was recrystallized three times from water, and phenylacetic acid three times from light petroleum, and kept in an evacuated desiccator for several hours. B.P. phenol and β-naphthol were used directly. Mercury was freshly distilled.

Oxygen was purified by passage through a liquid-oxygen trap, and nitrogen by passage over heated copper and through a liquid-oxygen trap.

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Syntheses using Monoketals of cyclo*Hexane*-1 : 2-*dione. Part II.** 2-*Ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dioxolan*), *the Corresponding Oxathiolan and Dithiolan, and Some Transformation Products thereof.*

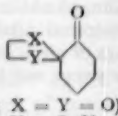
By (MRS.) R. H. JAEGER and HERCHEL SMITH.

[Reprint Order No. 5784.]

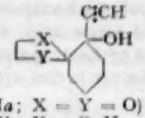
2-Ethynyl-2-hydroxy*cyclo*hexane-1-*spiro*-2′-(1′ : 3′-dioxolan) (II*a*) and the corresponding oxathiolan (II*b*) and dithiolan (II*c*) have been prepared by the action of lithium acetylide in liquid ammonia on 2-oxo*cyclo*hexane-1-*spiro*-2′-(1′ : 3′-dioxolan) and the corresponding oxathiolan and dithiolan. Treatment of (II*a*), (II*b*), and (II*c*) with formic acid and mercuriacetamide is described. The dehydration of the alcohols (II*b* and *c*) and the reaction of the resulting enynes with methanol in the presence of the boron trifluoride–mercuric oxide–trichloroacetic acid catalyst are recorded.

IN Part I* we described the synthesis and some features of the chemistry of the monoethylene ketals derived from *cyclo*hexane-1 : 2-dione. We now present an account of the preparation of the corresponding ethynylcarbinols and of some transformation products obtained from them.

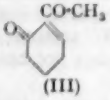
Reaction of the oxo-ketals (I*a*, *b*, and *c*) with lithium acetylide in liquid ammonia was slow, but satisfactory yields of the ethynylcarbinols (II*a*, *b*, and *c*) were obtained at room temperature and increased pressure, (I*a*) giving the lowest and (I*c*) the highest yield. The alcohol (II*b*) was obtained in both possible stereoisomeric forms. The infra-red spectrum of the minor, higher-melting isomer in solution in carbon tetrachloride has the hydroxyl



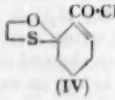
(I*a*; X = Y = O)
(I*b*; X = O, Y = S)
(I*c*; X = Y = S)



(II*a*; X = Y = O)
(II*b*; X = O, Y = S)
(II*c*; X = Y = S)



(III)



(IV)

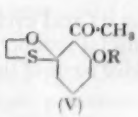
band at the longer wave-length (2·92 as against 2·86 μ), indicating a greater degree of hydrogen bonding in this isomer which probably has the hydroxyl group *cis* to the oxygen atom of the oxathiolan ring.

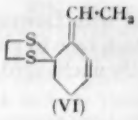
Treatment of the ethynylcarbinol (II*a*) with boiling formic acid, a reagent used for the dehydration of ethynylcarbinols and their rearrangement to αβ-unsaturated methyl

* Part I, *J.*, 1955, 160.

ketones (cf., *e.g.*, Hamlet, Henbest, and Jones, *J.*, 1951, 2657), afforded as the chief recognizable product 2-ethynyl*cyclo*hexanone, formed by hydrolysis of the ketal group. None of the desired product (III) was identified. Heating the carbinols (II*b* and *c*) with formic acid produced intractable tars.

Mercuriacetamide in methanol or ethanol, reagents which normally transform ethynylcarbinols into αβ-unsaturated methyl ketones (Aeschbacher and Goldberg, *Helv. Chim. Acta*, 1939, **29**, 1185; Birch and Robinson, *J.*, 1944, 503), gave no αβ-unsaturated ketone with the carbinols (II*a*, *b*, and *c*). Instead, the carbinol (II*b*), either as a mixture or in its pure lower-melting form, was converted in ethanol into a saturated ketone whose analysis corresponded to a compound formed by the addition of ethanol to the expected acetyl*cyclo*hexenone derivative (IV). The participation of the solvent in the reaction was confirmed when a similar experiment in methanol afforded a different ketone whose analysis indicated addition of methanol to (IV). By analogy with the known mode of addition of weak acids to conjugated mono-olefinic carbonyl compounds (Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London 1953, p. 690) the structures (V; R = Et and Me) were assigned to these ketones. The results of some desulphurization experiments also seem to support these formulations : when the compound (V; R = Me) was desulphurized with Raney nickel (Romo, Rosenkrantz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4961) no product could be isolated even after washing the nickel with ether containing acetic acid—a result consistent with the initial production in the reaction of an enolic β-diketone; when, however, the lithium aluminium hydride reduction product of


(V)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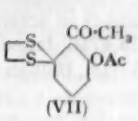
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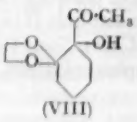
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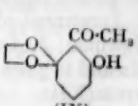
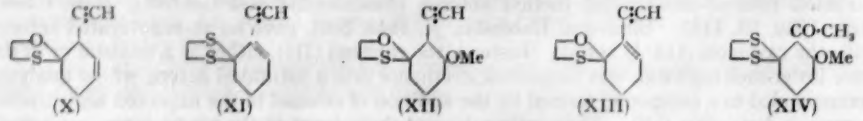

(IX)

(V; R = Me) was desulphurized in the same manner a saturated hydroxy-ketone was obtained which, on short treatment with Brady's reagent, gave a derivative having the correct analysis for the 2 : 4-dinitrophenylhydrazone of 2-1'-hydroxyethyl*cyclo*hex-2-enone. The major product of the action of mercuriacetamide in methanol or ethanol on the carbinol (II*c*) was an oxygen-free oil $C_{10}H_{14}S_2$ which, on the basis of its ultra-violet and infra-red absorption spectra, is a heteroannular conjugated diene not containing a terminal vinyl group. If, as seems most probable, no change in ring structure has occurred, this can only be (VI). A small amount of an acetoxy-ketone, formulated as (VII) by analogy with (V), was also isolated from the reaction. The alcohol (II*a*) gave with mercuriacetamide in ethanol a low yield of a hydroxy-ketone which is either (VIII) or, since it is in accord with the behaviour of the reagent with (II*b* and *c*), more probably (IX). The hydroxy-ketone reacted with thionyl chloride in pyridine at room temperature but no satisfactory product resulted.

Dehydration of the alcohols (II*b* and *c*) could not be achieved with phosphorus oxychloride in pyridine (Hamlet *et al.*, *loc. cit.*) even at reflux temperature, and was finally effected with the same reagent in collidine at 120—140°. The enyne from (II*b*) exhibited in the infra-red absorption spectrum a maximum at 6·0 μ consistent with an unconjugated double bond, and showed no selective light absorption in the range 220—320 mμ; it must therefore be (X). That from (II*c*) had an infra-red absorption maximum at 6·20 μ (conjugated double bond) and a light absorption maximum at 250 mμ, and is therefore (XI). The latter maximum is at a longer wave-length than would be expected for a vinylacetylene (cf. Hamlet *et al.*, *loc. cit.*) but the displacement to longer wave-length could be explained by steric strain in the chromophore (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273). We have advanced elsewhere (*Chem. and Ind.*, 1954, 1106) a tentative steric explanation for the different behaviour of the alcohols (II*b* and *c*) on dehydration. The demonstrated instability and therefore high reactivity of a double bond αβ to an oxathiolan ring may be used to explain why (II*b*) does not give an αβ-unsaturated ketone with mercuriacetamide in alcohols. It is predictable that such a ketone, if formed, would tend to add a suitable available weak acid, in this case an alcohol.

The enyne (X) on treatment with methanol in the presence of the boron trifluoride–mercuric oxide–trichloroacetic acid catalyst (Hamlet *et al.*, *loc. cit.*) gave three products. Two of these were isomeric ethynes resulting from the addition of methanol to (X); they formed mixed crystals and were separable by chromatography on alumina. We offer no proof of their structure, but in view of the experimentally demonstrated instability of a



(X) (XI) (XII) (XIII) (XIV)

double bond αβ to an oxathiolan ring and the known electronic effect of the ethynyl group which is electron-attracting relative to the vinyl group (Ingold, *op. cit.*, p. 71), it is reasonable to predict that they are isomers of (XII) formed by the addition of methanol to (XIII). The latter, under the acid conditions of the reaction, would be in equilibrium with (X). The third product was a methoxy-ketone possessing an infra-red absorption spectrum closely resembling that of (V; R = Me) and an indefinite melting point undepressed by (V; R = Me) from which it appears to be a mixture of stereoisomers of that compound. As might be expected from the observed greater stability of a double bond αβ to the dithiolan ring, the conjugated enyne (XI) added methanol under similar conditions much less readily than (X). Most of (XI) was recovered unchanged, but a small quantity of a compound $C_{11}H_{18}O_2S_2$, possibly (XIV), was obtained.

Treatment of the alcohols (II*a*, *b*, and *c*) in acetic acid with Dowex-50 in its acid cycle (Newman, *J. Amer. Chem. Soc.*, 1953, **75**,4740) failed in each case to give a useful product; (II*a* and *b*) gave complex mixtures, and (II*c*), though mostly unchanged, yielded some of the enyne (XI).

Experimental

Light petroleum without further definition means the fraction of b. p. 60—80°. Infra-red spectra of solids were determined for Nujol mulls except where stated otherwise. Spectra were determined by Dr. F. B. Strauss with the technical assistance of Mr. F. Hastings.

2-*Ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dioxolan*) (II*a*).—2-Oxo*cyclo*hexane-1-*spiro*-2′-(1′ : 3′-dioxolan) (7·16 g.) in tetrahydrofuran (50 c.c.) was added to a solution of lithium acetylide (from the metal, 2·9 g.) in liquid ammonia (600 c.c.) contained in a stainless-steel autoclave which was then closed. After 20 hr. the autoclave was cooled in solid carbon dioxide–methanol and opened. Ammonium chloride (22 g.) was added in small portions, followed by ether (200 c.c.) and water (500 c.c.). The ethereal layer was separated, and the aqueous layer thoroughly extracted with ether (4 × 400 c.c.). The extracts were combined, washed with water (200 c.c.), treated with small pieces of solid carbon dioxide, and dried (Na_2SO_4). Evaporation under reduced pressure afforded an oil (6·0 g.) which gave a copious precipitate with ammoniacal silver nitrate solution. It was dissolved in benzene–light petroleum (1 : 1; 50 c.c.) and adsorbed on activated alumina (180 g.). Elution with benzene–light petroleum (1 : 1; 500 c.c.) and benzene (1000 c.c.) gave unchanged ketone (2·5 g.); elution with benzene–ether (9 : 1; 1000 c.c.) gave a mixture of unchanged ketone and acetylenic material (0·63 g.); and elution with benzene–ether (2 : 3; 500 c.c.), benzene–ether (1 : 4; 500 c.c.), and ether (500 c.c.) gave the 2-*ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dioxolan*) (II*a*) (2·4 g.), b. p. 95—100° (bath-temp.)/0·2 mm. (Found: C, 65·7; H, 7·9. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·7%). The infra-red spectrum had bands at 2·88, 3·08, and 4·77 μ. With Brady's reagent the oil gave a 2 : 4-dinitrophenylhydrazone, m. p. 212—213° after recrystallisation from tetrahydrofuran.

2-*Ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (II*b*).—2-Oxo*cyclo*hexane-1-*spiro*-2′-(1′ : 3′-oxathiolan) (6·45 g.) in tetrahydrofuran (100 c.c.) was added to a solution of lithium acetylide (from the metal, 1·43 g.) in liquid ammonia (500 c.c.) contained in a rocking autoclave. The mixture was shaken for 48 hr., the autoclave cooled as before and opened, and after the addition of ammonium chloride (11 g.) the product was worked up as under (II*a*). The oily product (6·4 g.) was taken up in benzene–light petroleum (1 : 1; 30 c.c.) and adsorbed on activated alumina (150 g.). Elution with benzene–light petroleum (1 : 1; 1000 c.c.) gave unchanged ketone; elution with benzene–light petroleum (3 : 1; 500 c.c.), benzene (500 c.c.), benzene–ether (9 : 1; 500 c.c.) and benzene–ether (7 : 3; 500 c.c.) gave 2-*ethynyl*-2-*hydroxy*-

cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (II*b*) (2·35 g.), obtained from light petroleum as rhombs, m. p. 68° (Found : C, 60·7; H, 6·9; S, 16·0. $C_{10}H_{14}O_2S$ requires C, 60·6; H, 6·9; S, 16·2%). The infra-red spectrum had bands at 2·89, 3·09, and 4·75 μ; the spectrum in carbon tetrachloride had bands at 2·86 and 3·03 μ. Elution with benzene–ether (1 : 1; 500 c.c.) and ether (500 c.c.) gave a mixture of stereoisomers of (II*b*) as a viscous oil (0·94 g.), b. p. 110° (bath-temp.)/0·25 mm. (Found : C, 60·4; H, 6·9; S, 16·3%).

When the oily mixture of stereoisomers was treated with the Newman catalyst (*loc. cit.*) in acetic acid, and the product chromatographed on " Florex," light petroleum–benzene (3 : 1) eluted the remaining *stereoisomer* which crystallized from light petroleum as needles, m. p. 109—111° (Found : C, 60·3; H, 7·0; S, 16·2%). The infra-red spectrum had bands at 2·98, 3·06, and 4·76 μ; the spectrum in CCl_4 had bands at 2·92 and 3·03 μ.

2-*Ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dithiolan*) (II*c*).—2-Oxo*cyclo*hexane-1-2-*spiro*-2′-(1′ : 3′-dithiolan) (8·2 g.) in tetrahydrofuran (100 c.c.) was treated with lithium acetylide (from the metal, 1·6 g.) in liquid ammonia (600 c.c.) in an autoclave as before. After 48 hr. the autoclave was cooled and opened, and ammonium chloride (14 g.) was added followed by ether (250 c.c.) and water (500 c.c.). The ethereal solution was separated, and the aqueous layer extracted with benzene–ether (1 : 1; total 2 l.). The combined extracts after evaporation under reduced pressure afforded an oil (8·16 g.) which was dissolved in boiling light petroleum (b. p. 80—100°). On cooling, the solution deposited the 2-*ethynyl*-2-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dithiolan*) (II*c*) as rhombs (4·6 g.), m. p. 79·5° after recrystallisation from light petroleum (b. p. 80—100°) (Found : C, 55·8; H, 6·1; S, 30·25. $C_{10}H_{14}OS_2$ requires C, 56·1; H, 6·5; S, 29·9%). The infra-red spectrum had bands at 2·93, 3·08, and 4·76 μ.

2-*Ethynyl*-2-*hydroxy*cyclo*hexan*-1-*one*.—The ethynylcarbinol (II*a*) (0·87 g.) was refluxed with formic acid (10 c.c.; 90%) in an atmosphere of nitrogen for 1 hr. The dark mixture was poured on crushed ice, and the product collected in ether. The resulting brown oil was chromatographed in benzene–light petroleum (1 : 4; 10 c.c.) on acid-washed alumina (20 g.). Elution with light petroleum gave a partially crystalline oil A, and elution with mixtures of benzene–light petroleum (1 : 4 to 1 : 1) yielded the 2-*ethynyl*-2-*hydroxy*cyclo*hexane*-1-*one*, obtained from light petroleum as needles (0·16 g.), m. p. 50—52° (micro-hot stage), b. p. 130° (bath-temp.)/18 mm. (Found : C, 69·4; H, 7·6. $C_8H_{10}O_2$ requires C, 69·5; H, 7·3%). The partially crystalline oil A was rechromatographed in benzene–light petroleum on acid-washed alumina (4 g.). Elution with light petroleum gave an oil which on treatment with Brady's reagent yielded a 2 : 4-dinitrophenylhydrazone as a brick-red powder, m. p. 285° (decomp.) (Found : C, 41·1; H, 2·8%). Light absorption (in dioxan) : Max. 410 mμ; $\varepsilon \geqslant 26{,}000$ (substance only partially dissolved). Elution with mixtures of benzene and light petroleum (1 : 4 and 2 : 3) gave a further quantity (0·09 g.) of 2-ethynyl-2-hydroxy*cyclo*hexan-1-one.

Reaction of Mercuriacetamide in Alcohols with the Alcohols (II*a*, *b*, and *c*).—(i) The ethynylcarbinol (II*a*) (0·7 g.) was refluxed in 95% ethanol (25 c.c.) with mercuriacetamide (2·56 g.) for 6 hr. A little " Celite 545 " was added, and a stream of hydrogen sulphide passed through the suspension for 30 min. The solvent was removed under reduced pressure, and the residue repeatedly extracted with boiling ether. The combined extracts were washed with water to remove acetamide, dried (Na_2SO_4), and evaporated under reduced pressure to an oil (0·39 g.) which was taken up in light petroleum–benzene (3 : 1; 10 c.c.) and adsorbed on activated alumina (10 g.). The column was washed with light petroleum–benzene (2 : 1; 150 c.c.), then with light petroleum containing increasing proportions of benzene. Elution with benzene (150 c.c.) and benzene–ether (9 : 1; 300 c.c.) gave what is probably 2-*acetyl*-3-*hydroxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dioxolan*) (IX), obtained from light petroleum as needles (105 mg.), m. p. 82° (Found : C, 60·3; H, 8·1. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%). The infra-red absorption spectrum had bands at 2·90 and 5·88 μ. When the above experiment was carried out in commercial absolute ethanol a smaller yield of (IX) was obtained.

(ii) The ethynylcarbinol (II*b*), m. p. 68° (0·52 g.), was refluxed in ethanol (20 c.c.) with mercuriacetamide (0·91 g.) for 5·5 hr. Working up in the above manner gave an oil (0·49 g.) which was taken up in light petroleum (5 c.c.)–benzene (5 c.c.) and adsorbed on activated alumina (20 g.). The column was first washed with light petroleum (50 c.c.) and eluted with the same solvent (250 c.c.), then with light petroleum containing increasing amounts of benzene, and finally with pure benzene (100 c.c.). These eluates contained the same crystalline material, which was recrystallised from light petroleum to give 2-*acetyl*-3-*ethoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (V; R = Et) (0·19 g.), m. p. 119·5° (Found : C, 58·9; H, 7·9; S, 13·1. $C_{12}H_{20}O_3S$ requires C, 59·0; H, 8·2; S, 13·1%). The infra-red spectrum had a band at 5·88 μ. The alcohol (II*b*) (0·5 g.) in boiling methanol (30 c.c.) with mercuriacetamide (1·75 g.) (5·5 hr.)

gave similarly 2-*acetyl*-3-*methoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (V; R = Me) (0·255 g.), m. p. 138° (Found: C, 57·4; H, 7·6; S, 13·9. $C_{11}H_{18}O_3S$ requires C, 57·4; H, 7·8; S, 13·9%). The infra-red spectrum had a band at 5·90 μ.

(iii) The ethynylcarbinol (II*c*) (0·5 g.) was refluxed in ethanol (25 c.c.) with mercuriacetamide (1·55 g.) for 3·5 hr. Working up in the usual way gave an oil (0·39 g.) which was taken up in light petroleum (15 c.c.) and adsorbed on "Florex" (15 g.). Elution with light petroleum (50 c.c.) gave 2-*ethylidene*cyclo*hex*-3-*ene*-1-spiro-2′-(1′ : 3′-*dithiolan*) (VI) as an oil (0·24 g.), b. p. 150—160° (bath-temp.)/15 mm. (Found: C, 60·1; H, 6·6; S, 32·9. $C_{10}H_{14}S_2$ requires C, 60·6; H, 7·1; S, 32·9%). Light absorption (in MeOH): Max. 235 mμ (ε 8600). The infra-red spectrum had bands at 6·06 and 6·17 μ; there was no band in the 5·5 or 11 μ region. The column was eluted with a further quantity of light petroleum (50 c.c.) and with light petroleum containing increasing amounts of benzene. Elution with pure benzene (50 c.c.) gave what is probably 3-*acetoxy*-2-*acetyl*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dithiolan*) (VII), obtained from light petroleum as needles (0·06 g.), m. p. 110° (Found: C, 52·7; H, 6·5; S, 23·65. $C_{12}H_{18}O_3S_2$ requires C, 52·6; H, 6·6; S, 23·4%). The infra-red spectrum had bands at 5·76 and 5·85 μ. The same mixture was obtained when the above reaction was carried out in methanol.

2-1″-*Hydroxyethyl*-3-*methoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*).—The spiran (V; R = Me) (0·44 g.) was reduced with lithium aluminium hydride (0·22 g.) in pure ether (30 c.c.). The oily product (0·44 g.) was taken up in light petroleum (10 c.c.) and adsorbed on alumina (8 g.). Elution with light petroleum (100 c.c.), light petroleum containing increasing amounts of benzene, benzene (50 c.c.), and benzene–ether (9 : 1; 50 c.c.) all gave the 2-1″-*hydroxyethyl*-3-*methoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (130 mg.) which after recrystallisation from light petroleum had m. p. 135° (Found: C, 57·1; H, 8·6; S, 13·8. $C_{11}H_{20}O_3S$ requires C, 56·9; H, 8·6; S, 13·8%). The infra-red absorption spectrum had a band at 2·91 μ. Elution with benzene–ether (1 : 1; 100 c.c.) and ether (100 c.c.) gave a mixture of the above hydroxy-compound and an oil which was not identified. Light absorption for the mixture (in MeOH): Max. 230 and 277 mμ (ε 10,000 and 2000).

The above hydroxyethylmethoxy*cyclo*hexane-*spiro*-oxathiolan (100 mg.) was refluxed with W-2 Raney nickel (1·2 g.) in acetone (30 c.c.) for 3·5 hr. The product was an oil, the infra-red spectrum of which had bands at 2·90, 5·80, 8·22, and 8·45 μ. On treatment with Brady's reagent for 2 min. on the steam-bath it gave 2-1′-*hydroxyethyl*cyclo*hex*-2-*en*-1-*one* 2 : 4-*dinitrophenylhydrazone*, m. p. 194—196° after recrystallisation from ethyl acetate (Found: C, 52·5; H, 5·1. $C_{14}H_{16}O_5N_4$ requires C, 52·5; H, 5·0%). Light absorption (in $CHCl_3$): Max. 390 mμ (ε 31,000).

2-*Ethynyl*cyclo*hex*-3-*ene*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (X).—The ethynylcarbinol (II*b*) (1·22 g.) in collidine (10 c.c.) was stirred with phosphorus oxychloride (1 c.c.) at 120—130° under nitrogen for 1·25 hr. The mixture was cooled in ice, and ether (30 c.c.) was added followed by crushed ice. The ethereal layer was separated, and the aqueous layer extracted with ether (total 100 c.c.). The combined extracts were washed with 2N-sulphuric acid (200 c.c.), sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). The oily product was taken up in light petroleum (15 c.c.) and adsorbed on activated alumina (36 g.). Elution with light petroleum (400 c.c.) gave the 2-*ethynyl*cyclo*hex*-3-*ene*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (X), obtained from light petroleum as needles (0·49 g.), m. p. 59° (Found: C, 66·8; H, 6·7; S, 17·8. $C_{10}H_{12}OS$ requires C, 66·7; H, 6·7; S, 17·8%): no selective light absorption in the range 220—320 mμ. The infra-red spectrum had bands at 3·08, 4·76, and 6·0 μ.

2-*Ethynyl*cyclo*hex*-2-*ene*-1-spiro-2′-(1′ : 3′-*dithiolan*) (XI).—The ethynylcarbinol (II*c*) (3 g.) in collidine (25 c.c.) was stirred at 130—140° with phosphorus oxychloride under nitrogen for 1·5 hr. Working up as above gave a partially crystalline product (2·26 g.) which was dissolved in light petroleum–benzene (4 : 1; 25 c.c.) and adsorbed on activated alumina (25 g.). Elution with light petroleum (b. p. 40—60°; 250 c.c.) gave 2-*ethynyl*cyclo*hex*-2-*ene*-1-spiro-2′-(1′ : 3′-*dithiolan*) (XI) (1·62 g.), m. p. 78° after recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 61·3; H, 6·0; S, 32·6. $C_{10}H_{12}S_2$ requires C, 61·3; H, 6·1; S, 32·6%). Light absorption: Max. 250 mμ (ε 7800). The infra-red spectrum had bands at 3·07 and 6·22 μ.

Reaction of the Enynes (X) *and* (XI) *with Methanol in the Presence of a Boron Trifluoride–Mercuric Oxide–Trichloroacetic Acid Catalyst.*—(i) The catalyst was prepared in methanol (5 c.c.) from mercuric oxide (0·6 g.), trichloroacetic acid (0·45 g.), and the boron trifluoride–ether complex (0·2 c.c.) as described by Hamlet, Henbest, and Jones (*loc. cit.*), and 0·5 c.c. of this mixture was added to the enyne (X) (0·39 g.) in methanol (5 c.c.) which was then refluxed for 5 hr. and left at room temperature overnight. The solution was poured into 2N-hydrochloric acid (50 c.c.) and extracted with ether (total 150 c.c.). The ethereal solution was washed with sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4) and evaporated under

reduced pressure to an oil which was dissolved in light petroleum (10 c.c.) and adsorbed on activated alumina (12 g.). Elution with light petroleum (200 c.c.) and light petroleum–benzene (4 : 1; 50 c.c.) gave what is probably a stereoisomer of *2-ethynyl-3-methoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*oxathiolan*) (XII), obtained from light petroleum as needles (85 mg.), m. p. 95° (Found: C, 62·0; H, 7·4; S, 15·1. $C_{11}H_{16}O_2S$ requires C, 62·3; H, 7·6; S, 15·1%). The infra-red spectrum had bands at 3·08 and 4·76 μ. Elution with light petroleum–benzene (1 : 1; 50 c.c.), light petroleum–benzene (1 : 3; 50 c.c.), and benzene (50 c.c.) gave what is probably another *stereoisomer* of (XII), obtained from light petroleum as needles and plates (77 mg.), m. p. 118° (Found: C, 62·3; H, 7·4; S, 14·8%). The infra-red spectrum had bands at 3·11 and 4·77 μ. Elution with benzene–ether (9 : 1; 100 c.c.) gave what is probably a mixture of stereoisomers of 2-acetyl-3-methoxy*cyclo*hexane-1-*spiro*-2′-(1′ : 3′-oxathiolan) (V; R = Me) (53 mg.), which after recrystallisation from light petroleum had m. p. 110—118° (softening at *ca.* 90°) undepressed on admixture with the sample of (V; R = Me) prepared as above by the action of mercuriacetamide in methanol on (II*b*) (Found: C, 57·4; H, 7·5; S, 13·7. Calc. for $C_{11}H_{18}O_2S$: C, 57·4; H, 7·8; S, 13·9%). The infra-red spectrum had a band at 5·88 μ.

(ii) The enyne (XI) (0·3 g.) was refluxed for 5 hr. in methanol (5 c.c.) containing 0·4 c.c. of the above catalyst mixture. On cooling, the solution was added to 2N-hydrochloric acid and worked up as in (i). The oily product was taken up in light petroleum (10 c.c.) and adsorbed on activated alumina (7 g.). Elution with light petroleum (250 c.c.) gave unchanged (XI), obtained from light petroleum as needles (0·21 g.), m. p. 77°. Elution with light petroleum–benzene (3 : 1; 100 c.c.) gave an ill-defined oil, and elution with benzene–light petroleum (1 : 1; 100 c.c.) gave what is possibly 2-*acetyl*-3-*methoxy*cyclo*hexane*-1-spiro-2′-(1′ : 3′-*dithiolan*) (XIV), obtained from light petroleum (b. p. 40—60°) as needles (37 mg.), m. p. 52·5° (Found: C, 53·5; H, 7·2. $C_{11}H_{18}O_2S_2$ requires C, 53·7; H, 7·3%). The infra-red spectrum had a band at 5·89 μ.

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The Alkali-soluble Polysaccharides of the Lichen Cladonia alpestris (*Reindeer Moss*).

By G. O. Aspinall, E. L. Hirst, and (Mrs.) Margaret Warburton.

[Reprint Order No. 5818.]

A preliminary examination has shown that the alkali-soluble polysaccharides of reindeer moss (*Cladonia alpestris*) consist of mixtures of highly branched molecules containing residues of D-galactose, D-glucose, and D-mannose. Methylation studies have shown that the majority of the D-galactose and some of the D-glucose and D-mannose residues occupy terminal positions, while chains of D-glucose and of D-mannose residues constitute the backbone of the molecular structure. Periodate oxidation provides further evidence for complex highly branched structures.

The lichen *Cladonia alpestris*, commonly known as reindeer moss, is one of three closely related species, *C. alpestris*, *C. rangiferina*, and *C. sylvatica*, of common occurrence in Norway. Little is known concerning their composition but Professor Berner and his colleagues at Oslo University showed that reindeer moss, which contains 93% of carbohydrates, gives glucose, galactose, and mannose on hydrolysis (personal communication). This lichen appeared to differ considerably from Iceland moss (*Cetraria islandica*), the polysaccharides of which have been extensively investigated and have been shown to consist predominantly of D-glucose residues (Granichstädten and Percival, *J.*, 1943, 54; Meyer and Gürtler, *Helv. Chim. Acta*, 1947, **30**, 751, 761; Chanda and Hirst, unpublished work), although small quantities of D-galactose and D-mannose have been reported in the hydrolysates of some polysaccharide fractions. In the present investigation the alkali-soluble polysaccharides of *C. alpestris* have been examined, preliminary experiments having

shown that after removal of lichen acids with aqueous sodium carbonate very little polysaccharide could be extracted with hot water.

Two polysaccharide preparations (I and II) were obtained by extraction of the lichen with cold 5% and 24% potassium hydroxide solution respectively. The polysaccharides, although differing in optical rotation, had similar physical properties and gave the same sugars (galactose, glucose, and mannose) on hydrolysis, but in different proportions. D-Galactose and D-mannose were identified in both hydrolysates by the formation of crystalline derivatives. Fractionation of polysaccharide I *via* the copper complex gave a polysaccharide of different composition, indicating the presence of at least two different molecular species, but repeated fractionation failed to resolve the mixture.

Conversion of each of the two polysaccharides into their fully methylated derivatives gave similar products, differing slightly in optical rotation, but giving on hydrolysis the same complex mixture of methylated sugars. The methylated polysaccharides were therefore combined for subsequent examination. The methylated sugars (fraction A) obtained on hydrolysis of the methylated polysaccharides were fractionated on cellulose, but in most of the fractions separation of the sugars was incomplete. Although 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose was the only sugar from fraction A to be identified by the formation of a crystalline derivative, evidence from optical rotations, paper chromatography, and demethylation indicated the presence also of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose, a mixture of tri-*O*-methyl derivatives of D-glucose and D-mannose including 2 : 3 : 6-tri-*O*-methyl-D-glucose, 2 : 4 : 6-tri-*O*-methyl-D-galactose, and a di-*O*-methyl-D-glucose (probably the 2 : 3-isomer). In addition to these products of hydrolysis two portions (B and C) resistant to acid hydrolysis were also encountered, one of them (C) coming out of solution during the treatment with aqueous acid. These fragments were hydrolysed under more vigorous conditions and the products were further fractionated. Fraction B was shown to be an incompletely methylated fragment composed of residues of D-mannose only. From the hydrolysis products 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose was characterised as the crystalline aniline derivative and 3 : 4-di-*O*-methyl-D-mannose was identified as the crystalline monohydrate; in addition, paper chromatography indicated the presence of a tri-*O*-methyl-D-mannose, a second di-*O*-methyl-D-mannose, and a mono-*O*-methyl-D-mannose. Fraction C was shown to be composed solely of D-glucose residues and in the mixture of methylated sugars given on hydrolysis 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose was identified.

The yield of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose indicates that the majority of D-galactose residues are present as non-reducing end-groups, while some of the D-glucose and D-mannose residues also occupy terminal positions. The isolation of the resistant fragments B and C indicates the presence of two main structural features, which are remarkable in this group of polysaccharides in that each consists of chains of one type of sugar residue only. It is not possible on the present evidence to decide whether D-galactose residues are linked to both types of molecular structure or only to one.

The results of periodate oxidation experiments are consistent with the view that polysaccharides I and II both contain mixtures of highly branched polysaccharides. Oxidation of the polysaccharides resulted in the formation of 1 mol. of formic acid per 3·7 and 3·0 hexose residues respectively, while both polysaccharides consumed 1·2 mols. of periodate per residue. Confirmation was thus obtained for the presence of a high proportion of non-reducing end-groups. Hydrolysis of the periodate-oxidised polysaccharides indicated the presence of unattacked glucose residues and also in smaller amount of unattacked mannose residues. The former observation suggests the presence in the polysaccharides of glucose residues linked through positions 1 and 3, in which case it seems probable that 2 : 4 : 6-tri-*O*-methyl-D-glucose was one component of the mixture of incompletely identified tri-*O*-methylhexoses isolated from the methylated polysaccharide hydrolysate. The latter observation would be expected if the 3 : 4-di-*O*-methyl-D-mannose, previously isolated, has structural significance and does not arise from incomplete methylation. It is interesting that a trace of galactose was also given on hydrolysis of the oxidised polysaccharide I, suggesting the presence of a small proportion of D-galactose residues linked through positions 1 and 3. This provides further evidence that the tri-*O*-methyl-D-galactose present among the methylated sugars was indeed the 2 : 4 : 6-isomer.

It is evident from these preliminary experiments that the alkali-soluble polysaccharides of reindeer moss contain highly branched complex structures. The results emphasize the necessity of applying new methods of fractionation before the number and detailed structure of the components present in this lichen can be established.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper with the following solvent systems: (A) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3; v/v; top layer) and (B) butan-1-ol–ethanol–water (4 : 1 : 5; v/v; top layer).

Isolation of Alkali-soluble Polysaccharides from Cladonia alpestris.—Extractive-free lichen was extracted successively with cold dilute sodium carbonate solution and boiling water to remove lichen acids and water-soluble polysaccharides, and the residue was extracted with cold 5% and 24% potassium hydroxide solutions. The alkaline extracts were poured into ethanol acidified with glacial acetic acid and the precipitated polysaccharides (I and II respectively) were dried by solvent exchange with ethanol and ether. Polysaccharide I, isolated in 2·2% yield, had $(\alpha)_D^{15}$ +43·9° (*c*, 0·4 in 2N-NaOH) and chromatographic examination of the hydrolysate (Flood, Hirst, and Jones, *J.*, 1948, 1679) in solvent (A) showed the presence of galactose (12·6%), glucose (51·7%), and mannose (34·2%). Polysaccharide II, isolated in 1·3% yield, had $[\alpha]_D^{15}$ +61·4° (*c*, 0·89 in 2N-NaOH) and chromatographic examination of the hydrolysate showed the presence of galactose (12·9%), glucose (39·7%), and mannose (47·4%). D-Galactose and D-mannose were identified in both hydrolysates by the formation of the methylphenylhydrazone (m. p. and mixed m. p. 176—178°) and the phenylhydrazone (m. p. and mixed m. p. 198—199°) respectively.

A sample of polysaccharide I was fractionated by precipitation of the copper complex formed on addition of Fehling's solution to a solution of the polysaccharide in aqueous sodium hydroxide, followed by decomposition of the copper complex with dilute hydrochloric acid and precipitation of the regenerated polysaccharide with ethanol. The regenerated polysaccharide gave on hydrolysis galactose (15·2%), glucose (28·2%), and mannose (49·8%). These results showed that polysaccharide I was inhomogeneous, but repeated fractionations *via* the copper complex failed to yield distinct components.

Methylation of Polysaccharides.—Polysaccharides I (6·6 g.) and II (3·8 g.) were each methylated fifteen times with methyl sulphate and sodium hydroxide solution and twice with methyl iodide and silver oxide. Methylated polysaccharide I had $[\alpha]_D^{17}$ +35° (*c*, 0·5 in $CHCl_3$) (OMe, 44·5%) and methylated polysaccharide II had $[\alpha]_D^{17}$ +24·5° (*c*, 0·6 in $CHCl_3$) (OMe, 44·0%). Samples of both methylated polysaccharides were hydrolysed and the hydrolysates were examined chromatographically by use of solvent (B) and shown to contain qualitatively similar mixtures of methylated sugars.

Hydrolysis of Methylated Polysaccharides and Separation of Methylated Sugars.—The mixture of methylated polysaccharides I (1·3 g.) and II (2·7 g.) was refluxed with methanolic 1% hydrogen chloride (400 c.c.) for 17 hr. An insoluble residue (0·1 g.) was separated, and the hydrolysate was neutralised with ethereal diazomethane and concentrated to a syrup. The syrup was hydrolysed on the water bath with N-hydrochloric acid (200 c.c.) for 8·5 hr., during which a flocculent solid (soluble in methanol) separated. The solid was re-treated with methanolic and aqueous hydrogen chloride but a residue (C), insoluble in hydrochloric acid, remained and was separated. The combined acid hydrolysates were neutralised with silver carbonate and concentrated to a syrup (A) (3·2 g.).

Syrup A was fractionated on cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum–butan-1-ol (7 : 3), saturated with water, as eluant to give five main fractions (see Table) together with a number of smaller fractions (combined wt., 48 mg.) which were only examined chromatographically and shown to contain mixtures of di- and mono-*O*-methylsugars. Elution of the cellulose with water gave a non-reducing syrup (B) (0·64 g.) which was examined separately. Examination of fraction AI showed it to contain only 32% of reducing sugar (hypoiodite oxidation) and demethylation (Hough, Jones, and Wadman, *J.*, 1950, 1702) showed that methyl ethers of galactose, glucose, and mannose were present. The fraction (0·37 g.) was rehydrolysed and part of the hydrolysate (0·20 g.) was separated on filter sheets (Whatman 3MM) by use of solvent B to give four fractions.

Fraction AI*a* travelled on the chromatogram at the same rate as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose and on demethylation gave mannose. Quantitative paper chromatography (Hirst, Hough, and Jones, *J.*, 1949, 298) showed that tetra- and tri-*O*-methylhexoses were present in

fraction AI*b* in the ratio 2 : 1. The presence of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose in this fraction was shown by conversion into the aniline derivative, m. p. and mixed m. p. 186—189°. Demethylation of fraction AI*e* gave mannose and glucose, indicating the presence of trimethyl ethers of both these sugars. Fraction AII was chromatographically homogeneous and was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 189—191° (Found : OMe, 39·6. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9%).

Fraction	Wt. of material eluted (mg.)	$[\alpha]_D^{17}$ (solvent) *	Found : OMe (%)	Calc. : OMe (%)	Paper chromatography R_G in solvent B	Sugar
AI	799	+49·7° (W)	45·0	—	0·95	—
AI*a*	40	+23 (W)	49·0	52·5	1·00	Tetra-*O*-methylmannose
AI*b*	32	+53 (W)	46·1	—	1·00 0·93	,, Tetra-*O*-methylgalactose
					0·83	Tri-*O*-methylhexose
AI*c*	52	+22·4 (W)	43·7	41·9	0·83	,,
AI*d*	6	—	—	—	0·63	Di-*O*-methylhexose
AII	333	+109 (W) +76·3 (E)	50·1	52·5	0·91	Tetra-*O*-methylgalactose
AIII	483	+56·5 (W)	39·8	41·9	0·84	Tri-*O*-methylhexose
AIV	132	+80·4 (W)	36·7	—	0·71	Tri-*O*-methylgalactose
					0·65	Di-*O*-methylglucose
AV	66	+55·3 (W)	29·6	29·8	0·65	,,

* W = H_2O, E = EtOH.

The presence of trimethyl ethers of glucose and mannose in fraction AIII was shown by demethylation. The fall in rotation of the fraction in methanolic 1% hydrogen chloride at room temperature, $[\alpha]_D^{17}$ +50° → +27° (*c*, 0·2), indicated that 2 : 3 : 6-tri-*O*-methyl-D-glucose was one component of the mixture. {Under similar conditions 2 : 3 : 6-tri-*O*-methyl-D-glucose showed $[\alpha]_D$ +70° → −37° and 2 : 3 : 6-tri-*O*-methyl-D-mannose showed $[\alpha]_D^{17}$ +11° (const.)}. A sample of fraction AIII was oxidised with sodium metaperiodate but the absence of formaldehyde as shown by the Rimini ferricyanide–phenylhydrazine test (*Bull. Soc. chim.*, **1898**, **20**, 896) indicated the absence of 2 : 3 : 4-tri-*O*-methylhexose. The presence in fraction AIII of a small quantity of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, which had escaped chromatographic detection, was shown by formation of the aniline derivative, m. p. and mixed m. p. 185—187° : no other crystalline aniline derivatives were isolated. Fraction AIV contained two sugars travelling on the chromatogram at the same rate as 2 : 4 : 6-tri-*O*-methyl-D-galactose and 2 : 3-di-*O*-methyl-D-glucose and gave on demethylation galactose and glucose. Quantitative paper chromatography and calculation from the optical rotations showed that the relative proportion of the two sugars was 7 : 3. Fraction AV was chromatographically homogeneous, travelling at the same rate as 2 : 3-di-*O*-methyl-D-glucose, and gave glucose on demethylation.

Examination of Non-reducing Syrup B.—Syrup B had $[\alpha]_D^{17}$ +30° (*c*, 0·5 in H_2O) (Found : OMe, 31·8%) and on demethylation gave only mannose. A portion (0·45 g.) was hydrolysed on the water-bath successively with formic acid (45 c.c.; 95%) for 6·5 hr. and with N-sulphuric acid (30 c.c.) for 3 hr. The hydrolysate was neutralised with barium carbonate, and concentrated to a syrup (0·381 g.), part of which (0·320 g.) was fractionated on cellulose to give five main fractions BI—V. A number of smaller fractions (combined wt. 66 mg.) and a resistant residue (119 mg.), eluted with water, were not examined further.

Fraction BI (41·4 mg.) had $[\alpha]_D^{17}$ +21·7° (*c*, 0·8 in $CHCl_3$) and travelled on the chromatogram at the same rate as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-mannose. It was identified by conversion into 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-mannosylamine, m. p. and mixed m. p. 143—145°. Fraction BII (30 mg.) had $[\alpha]_D^{17}$ +14·5° (*c*, 0·6 in $CHCl_3$) and $[\alpha]_D^{17}$ +8·7° (*c*, 0·5 in H_2O), and travelled on the chromatogram at the same rate as 2 : 3 : 6-tri-*O*-methyl-D-mannose. Fraction BIII (30 mg.) crystallised and after recrystallisation from ethanol had m. p. and mixed m. p. (with authentic 3 : 4-di-*O*-methyl-D-mannose monohydrate) 78—80° and $[\alpha]_D^{17}$ +5° (*c*, 0·6 in H_2O; equil.). The two samples gave identical *X*-ray crystal photographs (by the courtesy of Dr. C. A. Beevers) and it is concluded that the authentic specimen, which originally had m. p. 109° (Haworth, Hirst, and Isherwood, *J.*, **1937**, 784), had changed to a more stable crystalline form with m. p. 80—82°. Fraction BIV (20 mg.) had $[\alpha]_D^{17}$ +7·5° (*c*, 0·4 in acetone) and R_G 0·62 in solvent B (3 : 4-di-*O*-methyl-D-mannose had R_G 0·65). Fraction BV (27 mg.) had $[\alpha]_D^{17}$ −5·3° (*c*, 0·3 in H_2O) and R_G 0·32 in solvent B, corresponding to a mono-*O*-methyl-D-mannose.

Examination of Residue C.—The solid C (0·5 g.) was hydrolysed on the water-bath successively

with formic acid (10 c.c.; 95%) for 7 hr. and with N-sulphuric acid (3 c.c.) for 6 hr., considerable decomposition occurring. After neutralisation with barium carbonate, the hydrolysate was concentrated to a syrup (0·250 g.), demethylation of which gave glucose only. A portion of the syrup (110 mg.) was separated on filter sheets with solvent B to give four fractions.

Fraction CI (30 mg.) crystallised and after recrystallisation from ether had $[\alpha]_D^{17}$ +80° (*c*, 0·3 in H_2O) and m. p. and mixed m. p. (with authentic 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose) 86—88°. Fraction CII (12 mg.) had $[\alpha]_D^{17}$ +68° (*c*, 0·2 in acetone) and R_G 0·86 in solvent B. The rotation of the fraction in methanolic 1% hydrogen chloride, $[\alpha]_D^{17}$ +33° (*c*, 0·2), indicated that 2 : 3 : 6-tri-*O*-methyl-D-glucose was one component of a mixture of tri-*O*-methyl-D-glucoses. {All other tri-*O*-methyl-D-glucopyranoses show $[\alpha]_D$ *ca.* +70° in methanolic hydrogen chloride (Granichstädten and Percival, *loc. cit.*).} Fraction CIII (35 mg.) travelled on the chromatogram at the same rate as 2 : 3-di-*O*-methyl-D-glucose but the optical rotation {$[\alpha]_D^{17}$ = +76° (*c*, 0·7 in acetone)} was higher than that quoted for 2 : 3-di-*O*-methyl-α-D-glucose {$[\alpha]_D^{17}$ = +81·9° → +48·3° in acetone (Irvine and Scott, *J.*, 1913, **103**, 575)}. Fraction CIV (16 mg.) had R_G 0·34 in solvent B, corresponding to a mono-*O*-methyl-D-glucose, but was not examined further.

Periodate Oxidation of Polysaccharides.—Oxidation of polysaccharide I (50-mg. batches) with potassium metaperiodate solution by the method of Halsall, Hirst, and Jones (*J.*, 1947, 1399, 1427) yielded a constant amount of formic acid after 208 hr., corresponding to 1 mol. per 3·7 $C_6H_{10}O_5$ residues. Oxidation of polysaccharide II yielded formic acid corresponding to 1 mol. per 3·0 $C_6H_{10}O_5$ residues.

Oxidation of the polysaccharides with sodium metaperiodate solution showed that both polysaccharides consumed 1·2 mols. of periodate per $C_6H_{10}O_5$ residue. Chromatographic examination of the hydrolysates of the periodate-oxidised polysaccharides showed the presence of glucose and mannose (trace), and from polysaccharide I galactose (trace) also.

The authors gratefully record the interest taken by the late Dr. E. G. V. Percival in the early stages of this work. They thank Professor E. Berner and Dr. R. C. Menzies for the supply of reindeer moss, the University of Edinburgh for the award of a Post-graduate Studentship (to M. W.), and the Distillers Company Limited for a grant.

CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, October 25th*, 1954.]

Chelate Systems. Part III. Infrared Spectra of Flavanones and Flavones.*

By B. L. SHAW and T. H. SIMPSON.

[Reprint Order No. 5796.]

The carbonyl stretching frequencies of a number of flavanones and flavones are recorded. The frequency shifts caused by methoxyl groups and by the hydrogen-bonded systems involving the 3- and the 5-hydroxyl group are discussed.

IN Parts I and II * the use of partition chromatography in the study of hydrogen bonding was discussed and chelation of flavones recognised by deviations from characteristic R_M values. Hydrogen bonding has been more generally investigated by infrared spectroscopy (Baker, *Ann. Reports*, 1936, **32**, 285; Gordy, *J. Chem. Phys.*, 1940, **8**, 516; Flett, *J.*, 1948, 1441; Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068). Hergert and Kurth (*ibid.*, 1953, **75**, 1622) have measured the infrared light-absorption spectra of Nujol and perfluorohexane mulls of several polyhydroxy- and polyacetoxy-flavones and -flavanones, but since it is known that interactions in the solid phase can give rise to significant changes in absorption spectra, the study of simpler compounds of this class in dilute solution seemed desirable.

The infrared absorption spectra of carbon tetrachloride solutions of a number of flavanones and flavones have been measured and the carbonyl stretching frequencies are recorded in Table 1.

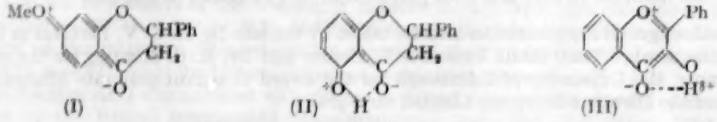
* Parts I and II, *J.*, 1952, 4268, 5027.

TABLE 1.

Compound	CO frequency, cm.$^{-1}$	Compound	CO frequency, cm.$^{-1}$
Flavanones		Flavones (*contd.*)	
(Unsubstd.)	1695	3-Hydroxy-	1619
7-Methoxy-	1685	5-Hydroxy-	1652
7 : 4′-Dimethoxy-	1686	3 : 5-Dihydroxy-	1638
5-Hydroxy-	1648	3-Hydroxy-7-methoxy-	1621
		3-Hydroxy-3′-methoxy-	1619
Flavones		3-Hydroxy-3′ : 4′-dimethoxy-	1616
(Unsubstd.)	1649	3-Hydroxy-7 : 3′-dimethoxy-	1616
7-Methoxy-	1640	*3-Hydroxy-7 : 4′-dimethoxy-	1611
3′-Methoxy-	1655	5-Hydroxy-7-methoxy-	1659
4′-Methoxy-	1653	5-Hydroxy-3′-methoxy-	1645
7 : 3′-Dimethoxy-	1638	5-Hydroxy-4′-methoxy-	1649
7 : 4′-Dimethoxy-	1646	5-Hydroxy-7 : 3′-dimethoxy-	1647
3′ : 4′-Dimethoxy-	1647	*7 : 3′ : 4′-Trimethoxy-	1638

* These compounds were not sufficiently soluble to give carbonyl absorption of greater than 20%. The reported frequencies may therefore be inaccurate.

Flavanones. From Table 1 it is seen that introduction of a methoxyl group in the 7-position of the flavanone nucleus causes a frequency shift of −10 cm.$^{-1}$, presumably due to the contribution of (I) to the resonance structure. The introduction of a 4′-methoxyl group, as expected, causes no further change. A hydroxyl group in the 5-position causes a larger frequency decrease (40 cm.$^{-1}$) resulting from the contribution of the chelated structure (II).



Flavones. Table 2 lists the differences between the carbonyl stretching frequencies of substituted flavones and the corresponding flavanones. The unchelated compounds show the expected frequency decrease resulting from the increased conjugation of the carbonyl

TABLE 2.

Flavone substituent	None	7-MeO	7 : 4′-Di-OMe	5-OH
Frequency diff. (cm.$^{-1}$), flavone − flavanone	−36	−35	−40	+4

group. The small difference between the carbonyl frequencies of 5-hydroxyflavone and 5-hydroxyflavanone is due to the unusual properties of the former chelated system (see below). All the 3-hydroxyflavones examined showed only feeble absorption bands at about 3360 cm.$^{-1}$, suggesting partial suppression of hydroxylic character by internal hydrogen bonding. The shifts in carbonyl stretching frequency caused by the introduction of a hydroxyl group at the 3-position of the flavone nucleus are listed in Table 3.

TABLE 3.

Flavone substituents	Frequency shift (cm.$^{-1}$) on addition of 3-OH group	Flavone substituents	Frequency shift (cm.$^{-1}$) on addition of 3-OH group
None	−30	7 : 4′-Di-OMe-	−35
3′-OMe-	−36	7-OMe	−19
3′ : 4′-Di-OMe-	−31	7 : 3′-Di-OMe	−22

These again indicate chelation between the carbonyl and the 3-hydroxyl groups and are interpreted as in Part I (*loc. cit.*) by the stabilisation of ionic structure (III) (and similar forms) by hydrogen bonding (Rasmussen *et al.*, *loc. cit.*).

Chemical evidence, chromatographic data (Part I, *loc. cit.*), and the small depressions of melting point on admixture with water (Gallagher, Hughes, O'Donnell, Philbin, and Wheeler, *J.*, **1953**, 3770) clearly establish 5-hydroxyflavones as chelated compounds. Moreover, these compounds show no absorption in the region 3200—3700 cm.$^{-1}$. It is found, however (Table 4), that introduction of a 5-hydroxyl group into flavone *increases*

or at most only slightly decreases the carbonyl stretching frequency (cf. Hergert and Kurth (*loc. cit.*). In this respect, 5-hydroxyflavones differ from other *peri*-hydroxycarbonyl compounds; indeed, Flett (*J.*, 1948, 1441) suggests that the hydrogen bond strengths in 1-hydroxyanthraquinones can be calculated from the carbonyl frequency *decrease*. No adequate interpretation of these effects can be offered.

TABLE 4.

Flavone substituent	Frequency shift ($cm.^{-1}$) on addition of 5-OH group	Flavone substituent	Frequency shift ($cm.^{-1}$) on addition of 5-OH group
None	+3	4′-OMe	−4
7-OMe	+19	7 : 3′-Di-OMe	+9
3′-OMe	−10		

Introduction of a 5-hydroxyl group into 3-hydroxyflavone causes the absorption due to O–H stretching to be intensified and shifted to 3395 $cm.^{-1}$, indicating a decrease in overall hydrogen bonding. These observations are in agreement with the conclusion from chromatographic evidence (Part I, *loc. cit.*) that the two chelate systems are opposed. Table 5 shows the changes in carbonyl stretching frequencies caused by introduction of

TABLE 5.

Flavone substituent	Frequency shift ($cm.^{-1}$) on addition of 7-OMe group	Flavone substituent	Frequency shift ($cm.^{-1}$) on addition of 7-OMe group
None	−7	4′-OMe	−17
3′-OMe	−9	3′ : 4′-Di-OMe	−11

a 7-methoxyl group into unchelated flavones. As with flavanones, these decreases are ascribed to conjugation of methoxyl and carbonyl groups. Addition of the less conjugated 4′-methoxyl or the unconjugated 3′-methoxyl groups causes the expected small changes in carbonyl frequency, but these are of the same order as the expected errors in measurement.

Many of the compounds required for this investigation were already available to us, two were generously given by Professor T. R. Seshadri, and the remainder were synthesised by established methods.

EXPERIMENTAL

(a) *Infrared Light-absorption Spectra.*—Spectra were measured on the double-beam recording spectrometer with a rock-salt prism, described by Hales (*J. Sci. Instr.*, 1953, **30**, 52).

(b) *Preparation of Flavanones and Flavones.*—M. p.s were determined on a Kofler block and are corrected.

Methoxyflavones. These were prepared by oxidation of the appropriate chalkones with excess of selenium dioxide in boiling amyl alcohol. The products were isolated by steam-distillation of the solutions and repeated recrystallisation (from light petroleum, or benzene–light petroleum) of the residual solids.

5-Hydroxy-7 : 3′-dimethoxy- and -3′-methoxy-flavones. Methyl sulphate (2·8 ml.) was added to a solution of 5 : 3′-dihydroxy-7-methoxyflavone (Part II, *loc. cit.*, 110 mg.) in ethanol (20 ml.) and aqueous N-sodium carbonate (30 ml.). After 30 min., excess of water was added, and the solid repeatedly recrystallised from propanol. *5-Hydroxy-7 : 3′-dimethoxyflavone* formed needles (75 mg.), m. p. 132—133°, exhibiting a violet ethanolic ferric colour (Found : C, 68·7; H, 4·9. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). Its *acetate* formed colourless prisms, m. p. 155—157°, from ethanol (Found : C, 67·2; H, 4·6. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8%).

Methylated by the same procedure, 5 : 3′-dihydroxyflavone (Part II, *loc. cit.*) yielded its *3′-methyl ether* in colourless needles, m. p. 145—148°, from ethanol, giving a violet ethanolic ferric colour (Found : C, 71·7; H, 4·7. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). Its *acetate* formed colourless needles, m. p. 120—122°, from ethanol (Found : C, 69·8; H, 4·8. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·6%).

3-Hydroxy-7 : 3′-dimethoxyflavone. 2′-Hydroxy-3 : 4′-dimethoxychalkone (1 g.) in hot ethanol (10 ml.) and aqueous sodium hydroxide (8 g., in 10 ml. of water) was oxidised with 30% hydrogen peroxide (10 ml.). Isolated by the standard method, 3-hydroxy-7 : 3′-di-

methoxyflavone (von Kostanecki and Widmer, *Ber.*, 1904, **37**, 4159) was obtained in cream-coloured needles, m. p. 171—172°, from ethanol (Found: C, 68·8; H, 4·8. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·8%).

We are indebted to Professor T. R. Seshadri for generous gifts of 5-hydroxyflavanone and 3 : 5-dihydroxyflavone, and to Mr. J. L. Hales for determining the infra-red light-absorption spectra. One of us (B. L. S.) thanks the Department of Scientific and Industrial Research for a Senior Research Award.

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The Chemistry of Extractives from Hardwoods. Part XXI. The Structure of Eperuic Acid.*

By F. E. KING and GURNOS JONES.

[Reprint Order No. 5831.]

Eperuic acid, a new bicyclic diterpene carboxylic acid, $C_{20}H_{34}O_2$, is the chief constituent (*ca.* 85%) of an oleo-resin derived from the wallaba tree (*Eperua falcata* and other *Eperua* spp.) of British Guiana. The acid and its principal compounds are liquid.

Selenium dehydrogenation of the methyl ester, which can readily be prepared by the Fischer–Speier method, yields naphthalene derivatives, including 1 : 2 : 5-trimethylnaphthalene. The ozonolysis products of methyl eperuate are formaldehyde, formic acid, and a keto-ester $C_{20}H_{34}O_3$, and, when the latter is dehydrogenated, pimanthrene (1 : 7-dimethylphenanthrene) is obtained. These indications of a relation to the manoöl–agathic acid group of diterpenes were substantiated by stepwise oxidation of dihydro-eperuic acid, through an acid $C_{19}H_{34}O_3$ and methyl ketone $C_{18}H_{32}O$, to a C_{17} acid which yielded 1-ethyl-2 : 5-dimethylnaphthalene when aromatised and decarboxylated with selenium. Eperuic acid is therefore 5-(4-carboxy-3-methylbutyl)decahydro-1 : 1 : 10-trimethyl-6-methylenenaphthalene.

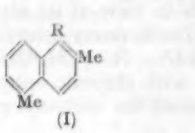
THE tropical American genus *Eperua*, principally *E. falcata*, which occurs extensively in British Guiana, is the source of a highly durable gummy timber commonly known as wallaba. The wood is used locally for constructional purposes and as fuel, and in view of its abundance has been examined for possible commercial applications, *e.g.*, for paper-making (*Bull. Imp. Inst.*, 1928, **26**, 4; 1930, **28**, 411) and as a tanning agent (F. Heim de Balsac, Deforge, and H. Heim de Balsac, *Halle aux Cuirs*, 1930, 369; Spoon, *Nederland Leder. Ind.*, 1941, **53**, 34, 1891). Treatment with boiling alcohol yields considerable amounts of a reddish phenolic resin, as much as 25% of the heartwood being removed in this way (Farmer and Campbell, *J. Soc. Chem. Ind.*, 1948, **67**, 233), but no chemically homogeneous constituent has so far been isolated from the timber or its extractives. From the living tree a further product is obtainable in the form of a pale viscous oleo-resin which is distinct from the phenolic material derivable from the wood by extraction with alcohol. An investigation of this resinous exudate, which was generously provided by Mr. R. S. Greathead, Messrs. Brown and Forth Ltd., London, has shown that approximately 85% is soluble in aqueous sodium carbonate and, as already briefly reported (*Chem. and Ind.*, 1953, 1325), consists of a new monocarboxylic diterpene, eperuic acid. The acid has also been extracted from the wood with boiling light petroleum and therefore appears to be a normal constituent of the tree.

The acid, which is lævorotatory, is conveniently purified through its readily distilled ester, methyl eperuate. Analysis of the acid, of the methyl ester, and of its lithium aluminium hydride reduction product, eperuyl alcohol—all liquids without crystalline derivatives—are consistent with a molecular formula $C_{20}H_{34}O_2$ for the parent compound. When catalytically reduced, methyl eperuate gives a dihydro-acid yielding a crystalline

* Part XX, *J.*, 1954, 4594.

p-bromophenacyl ester. Eperuic acid has no marked light absorption above 210 mμ, whence it follows that the ethylenic bond and carboxyl group are not in conjugation. Dihydroeperuic acid, $C_{20}H_{36}O_2$, is saturated in the tetranitromethane test; thus the terpene is bicyclic. The ease of esterification of eperuic acid, which occurs under Fischer–Speier conditions, and also of hydrolysis of the resultant ester, is in contrast to the behaviour of the known monocarboxylic diterpenes and the carboxyl group cannot therefore be situated in the usual sterically hindered 1-position.

Evidence as to the carbon skeleton of eperuic acid was obtained by dehydrogenation of the methyl ester with selenium, when, at 340—360°, 1 : 2 : 5-trimethylnaphthalene (I; R = Me) was obtained. Under somewhat less drastic conditions two other naphthalene derivatives were formed in which the greater part of the original molecule survived. One, a hydrocarbon $C_{17}H_{20}$, now appears to be identical with a product derived from agathic acid (II) (Ruzicka and Hosking, *Annalen*, 1929, **469**, 147) and very recently shown by synthesis (Büchi and Pappas, *J. Amer. Chem. Soc.*, 1954, **76**, 2963) to be 1 : 1 : 4 : 7-tetramethylperinaphthane (III). The other was an ester and on hydrolysis yielded a crystalline acid, $C_{18}H_{22}O_4$; when the constitution of eperuic acid became known it was possible to assign the structure (IV) to this dehydrogenation product.



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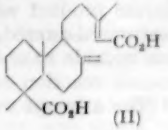

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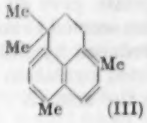

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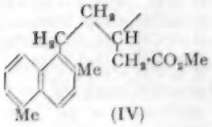

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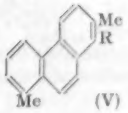

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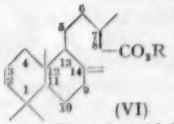


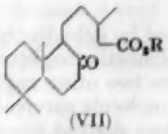
(VI)

Eperuic acid (R = H)

Ozonolysis of methyl eperuate gave a keto-ester, $C_{20}H_{34}O_3$, together with formaldehyde and formic acid, thus showing that the double bond terminates in a methylene group. A liquid acid, characterised by a crystalline oxime, was obtained by hydrolysis of the keto-ester. The keto-ester was also the principal product formed by permanganate oxidation of methyl eperuate, being then accompanied by a small quantity of crystalline dicarboxylic acid $C_{15}H_{24}O_4$. The constitution of the latter is unknown, and it is not clear whether this by-product is derived from eperuic acid or is the oxidation product of an undetected impurity.

Whereas naphthalene derivatives were obtained from the dehydrogenation of methyl eperuate, the action of selenium on the keto-ester, as well as on the corresponding hydroxy-ester prepared from it with lithium aluminium hydride, gave 1 : 7-dimethylphenanthrene (pimanthrene) (V; R = H) in good yield. This is attributed to the condensation of the keto-ester carbonyl group—or in the case of the hydroxy-ester, of the cation formed during the pyrolysis—with the carbon atom activated by its proximity to the methoxycarbonyl group, and it suggested a relation with the manoöl–agathic acid group of diterpenes. Formula (VI; R = H), bearing, as in agathic acid (II), a carboxyl group at position 19, was therefore tentatively adopted, and subsequently proved to be the correct structure for the new diterpene. Cyclisation of the derived keto-ester (VII; R = Me) and also of the hydroxy-ester (VIII; R = Me, R′ = OH) to pimanthrene during dehydrogenation is readily explicable on the basis of this formula. On the other hand, 14-demethyldihydroeperuic acid (VIII; R = R′ = H), which was prepared by Wolff–Kishner reduction of the keto-ester (VII; R = Me), under normal conditions of dehydrogenation gave a C_{17} tetralin, presumably (IX). Further treatment with selenium in a sealed tube at 355° yielded a small amount of fully aromatised material which from the properties of its trinitrobenzene adduct is believed to be 1-ethyl-5-methylnaphthalene.

Attempts were made to establish the position of the carboxyl group in eperuic acid by cyclising the keto-ester (VII; R = Me) to a tricyclic compound. Reduction—for example of carboxyl to methyl—should then avoid possible expulsion of the substituent during dehydrogenation, which, with (VI; R = H) as the structure of the diterpene, should lead ultimately to 1 : 2 : 8-trimethylphenanthrene (V; R = Me). The action of boiling acetic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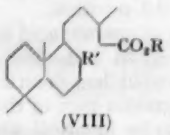
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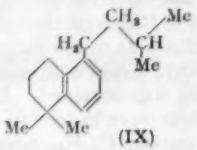
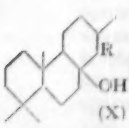

(IX)

anhydride and sodium acetate on the keto-ester resulted solely in the formation of an enol-acetate, but with sodium methoxide the keto-compound afforded the tricyclic hydroxy-ester (X; R = CO_2Me) together with an acidic substance having an intense ferric reaction and probably formed by Claisen condensation of the side-chain with one or other of the activated positions adjacent to the carbonyl group. Dehydration with heated potassium hydrogen sulphate gave an unsaturated liquid product which in view of its ultra-violet light absorption seemed to consist of αβ-unsaturated ester(s). The hydroxy-ester (X; R = CO_2Me) was reduced by lithium aluminium hydride to a diol (X; R = $CH_2{\cdot}OH$) which, however, resisted oxidation by the Oppenauer reaction and with chromic anhydride in pyridine gave the acid (X; R = CO_2H). The attempt to orient the carboxyl group by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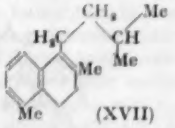
(XVII)

(XI) R = $CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH{:}CPh_2$
(XII) R = $CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$
(XIII) R = $CH_2{\cdot}CH_2{\cdot}CMe{:}CPh_2$
(XIV) R = $CH_2{\cdot}CH_2{\cdot}COMe$
(XV) R = $CH_2{\cdot}CH_2{\cdot}CO_2H$
(XVI) R = $CH_2{\cdot}CH{:}CPh_2$

this method was therefore abandoned in favour of an alternative, *viz.*, stepwise degradation of the acidic side-chain by the Barbier–Wieland procedure. The diphenylethylene (XI), a liquid prepared from methyl dihydroeperuate and excess of phenylmagnesium bromide, was not characterised but oxidised directly to the C_{19} acid (XII), also liquid but having a crystalline *p*-bromophenacyl ester. The methyl ester of (XII) yielded a solid diphenylethylene (XIII), and this was oxidised with ozone to a methyl ketone (XIV), thus establishing the relative position of the side-chain methyl group. Further oxidation, with sodium hypoiodite, degraded the ketone (XIV) to a crystalline C_{17} acid (XV) from which a solid diphenylethylene (XVI) was obtained in the usual way. The acid (XV), m. p. 134—135°, $[\alpha]_D$ −29·9°, is an isomer of that obtained from ambrein by Ruzicka and Lardon (*Helv. Chim. Acta*, 1946, **29**, 912), the latter, m. p. 136—137°, having $[\alpha]_D$ +33° (Dr. O. Jeger, personal communication).

With the intention of preparing a conjugated diene for the complete oxidative removal of the residual side-chain, the product (XVI) was treated with *N*-bromosuccinimide, but under the usual conditions it entirely failed to react. Selenium dehydrogenation of the acid (XV), however, gave the expected 1-ethyl-2 : 5-dimethylnaphthalene, as shown by the identity of its trinitrobenzene derivative with an authentic specimen, so confirming the structure attributed to eperuic acid on the basis of its resemblance to the manoöl–agathic acid group of diterpenes.

In the expectation that 2 : 5-dimethyl-1-*iso*pentylnaphthalene might be present among the dehydrogenation products of eperuic acid, this hydrocarbon was synthesised from 2 : 5-dimethyl-1-tetralone (Kipping and Wild, *J.*, 1940, 1238; Hosking and Ruzicka, *Helv. Chim. Acta*, 1930, **13**, 1412). When it was treated with *iso*pentyl-lithium (Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 1499) the dihydronaphthalene (XVII) was obtained which being difficult to dehydrogenate with selenium was oxidised with chloranil in boiling xylene (Campbell and Soffer, *ibid.*, 1942,

64, 422). The product (I; R = *iso*pentyl), a liquid, was characterised as a crystalline trinitrobenzene derivative.

Experimental

Unless otherwise stated, specific rotations were determined in $CHCl_3$.

Eperuic Acid (VI; R = H).—The wallaba oleo-resin (500 g.), an opaque honey-coloured viscous syrup, was dissolved in ether (2 l.), and the solution was stirred with excess of 0·5N-sodium carbonate. The terpene was then isolated from the aqueous solution, by acidification and ether-extraction, as a nearly colourless thick syrup, distillable in a high vacuum but more conveniently purified as the methyl ester, prepared by refluxing the product for 1 hr. with methanol (1 l.) containing concentrated sulphuric acid (8 c.c.). Most of the unused alcohol was then removed by evaporation from a steam-bath, and the residue was shaken with water and ether, unchanged eperuic acid (20—30 g.) being removed by washing with a solution of sodium carbonate. Distillation of the dried residue gave *methyl eperuate* (VI; R = Me) as a colourless mobile oil (*ca.* 420 g.), b. p. 164°/0·4 mm., $[\alpha]_D^{18}$ −28·2° (*c*, 3·98), n_D^{18} 1·4982, *d* 0·979, $[M_R]$ 95·5 (calc., 95·9) (Found: C, 78·7; H, 11·5. $C_{21}H_{36}O_2$ requires C, 78·8; H, 11·3%).

Hydrolysis of the ester with methanolic 2N-potassium hydroxide for 1 hr., evaporation of the solution, and treatment with mineral acid liberated *eperuic acid*, b. p. 190°/0·7 mm. (Found: C, 78·2; H, 11·3. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·3%). Its amide, anilide, and phenacyl and *p*-bromophenacyl esters were oily.

The brown gummy fraction of the exudate undissolved by aqueous sodium carbonate yielded a further quantity of eperuic acid (*ca.* 40 g.) after being refluxed with methanolic N-potassium hydroxide.

Eperuyl Alcohol.—Methyl eperuate (9 g.) and lithium aluminium hydride (1·5 g.), dissolved in equal volumes (70 c.c.) of ether, were slowly mixed and then heated under reflux for ½ hr. Addition of aqueous 2N-sodium hydroxide and evaporation of the ethereal solution yielded *eperuyl alcohol*, a colourless oil (6·5 g., 80%), b. p. 158°/1 mm., n_D^{18} 1·5068, *d* 0·953, $[M_R]$ 91·18 (calc., 91·64) (Found: C, 81·4; H, 11·8. $C_{20}H_{36}O$ requires C, 82·1; H, 12·3%).

A solution of the alcohol in benzene (50 c.c.), stirred with phosphorus tribromide (6·5 g.) for 3 hr. at 0—5°, gave *eperuyl bromide* which was isolated, after washing with sodium carbonate and water, as a colourless syrup, b. p. 124°/0·14 mm., n_D^{18} 1·514 (Found: C, 67·8; H, 9·9. $C_{20}H_{35}Br$ requires C, 67·6; H, 9·9%).

Methyl Dihydroeperuate (VIII; R = R′ = Me).—Methyl eperuate (6 g.), dissolved in acetic acid containing platinum oxide catalyst, readily absorbed hydrogen (430 c.c.; calc. for 1 double bond, 420 c.c.) at N.T.P. When the solution was filtered and distilled, *methyl dihydroeperuate* (5·5 g., 90%), b. p. 138—140°/0·1 mm., was obtained as a colourless oil, $[\alpha]_D^{25}$ −26·3° (*c*, 3·2), n_D^{18} 1·4902 [Found: C, 78·6; H, 11·8%; *M* (Rast), 317. $C_{21}H_{38}O_2$ requires C, 78·2; H, 11·9%; *M*, 322].

Dihydroeperuic Acid (VIII; R = H, R′ = Me).—Methyl dihydroeperuate (5 g.) was hydrolysed by refluxing methanolic N-potassium hydroxide (25 c.c.) for 1 hr. The *dihydro-acid* obtained by evaporating the liquid, acidifying and extracting it with ether, was a colourless viscous gum (4·15 g.), b. p. 186°/0·5 mm. (Found: C, 78·0; H, 11·9. $C_{20}H_{36}O_2$ requires C, 77·9; H, 11·8%). The *p-bromophenacyl ester* crystallised from dilute ethanol in plates, m. p. 71—71·5° (Found: C, 66·5; H, 8·0; Br, 15·9. $C_{28}H_{41}O_3Br$ requires C, 66·5; H, 8·0; Br, 15·8%).

Selenium Dehydrogenation of Methyl Eperuate.—(i) The methyl ester (10 g.) was heated with selenium (10 g.) in a metal bath at 280—300° for 30 hr. Distillation of the product, collected by means of ether, gave three principal fractions, the first (1·9 g.), b. p. 120—128°/2 mm., apparently consisting of incompletely dehydrogenated compounds (Found: C, 87·6; H, 11·6%).

The intermediate portion (3·5 g.), b. p. 140—150°/2 mm., was heated with 10% methanolic potassium hydroxide for 1 hr. and, after dilution with water, separated into alkali-soluble and -insoluble material, the latter being removed in ether. Acidification of the alkaline solution gave 1-(*4-carboxy-3-methylbutyl*)-2:5-*dimethylnaphthalene* crystallising as colourless needles (0·15 g.), m. p. 96°, from light petroleum; light absorption in ethanol: max. at 234, 280, 290, 325 mμ (log ε 4·05, 3·86, 3·92, 3·15) (Found: C, 80·0; H, 7·9%; equiv., 268. $C_{18}H_{22}O_2$ requires C, 30·0; H, 8·2%; equiv., 270).

The alkali-insoluble liquid gave a picrate which, crystallised from methanol, had m. p. 133° (Found: C, 60·5; H, 4·9; N, 9·2. Calc. for $C_{17}H_{20}.C_6H_3O_7N_3$: C, 60·9; H, 5·1; N, 9·3%); 1:1:4:7-tetramethylperinaphthane picrate (synthetic, Buchi and Pappas, *loc. cit.*) has m. p. 135·5—136° (*ex* agathic acid, Ruzicka and Hosking, *Helv. Chim. Acta*, 1930, **13**, 1402 give

138—139°). A sample of the hydrocarbon, b. p. (bath-temp.) 158°/2 mm., prepared from the recrystallised picrate had light absorption (in hexane): max. at 235, 290, 326 mμ (log ε 4·1, 3·84, 2·99).

The third fraction (0·8 g.), b. p. 160—165°/2 mm., dissolved in light petroleum and passed through a column of alumina, also yielded 1 : 1 : 4 : 7-tetramethylperinaphthane (III) (characterised as picrate), followed by a further small amount of ester of which the acid (as IV) (0·05 g.) was the hydrolysis product.

(ii) A mixture of methyl eperuate (5 g.) and selenium (5 g.) at 340—360° for 48 hr. yielded as the sole volatile material an oil (1·3 g.), b. p. 112°/0·05 mm. Its trinitrobenzene derivative formed orange needles (from ethanol), m. p. 154° alone or mixed with a specimen of 1 : 2 : 5-trimethylnaphthalene–trinitrobenzene adduct.

Oxidation of Methyl Eperuate.—(i) *With ozone.* A solution of methyl eperuate (7 g.) in methylene chloride (100 c.c.) was ozonised at −30° to −40° and the issuing gas passed into aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitate (0·54 g., 15%), crystallised from methanol, had m. p. 163—164° and was identified with the formaldehyde derivative by mixed m. p. and by paper chromatography (Meigh, *Nature*, 1952, **170**, 579).

The reaction mixture was treated with water (100 c.c.), and the methylene chloride removed by means of an air-stream and warming. It was condensed in traps cooled in solid carbon dioxide–alcohol, and washed with water, the washings yielding the crystalline dimedone derivative of formaldehyde, m. p. and mixed m. p. 186—187°. The mixture remaining after evaporation of the original solvent was heated with hydrogen peroxide (20 c.c. of 30%) for 1 hr., and the formic acid isolated by steam-distillation was titrated with sodium hydroxide (required 65% of theory) and characterised as *NN*-di-*p*-tolylformamidine hydrochloride (Whalley, *J.*, 1948, 1015), m. p. and mixed m. p. 264—266°.

The principal ozonolysis product—which was collected in ether, washed with aqueous sodium carbonate, and distilled—consisted of the liquid *keto-ester* (VII; R = Me) (5 g.), b. p. 141°/0·05 mm., n_D^{16} 1·4940 (Found: C, 74·7; H, 10·3. $C_{20}H_{34}O_3$ requires C, 74·5; H, 10·6%). Hydrolysis by refluxing it with methanolic 2N-potassium hydroxide for 2 hr. gave the parent acid characterised by an *oxime*, which crystallised from ethanol in needles, m. p. 223°, $[\alpha]_D^{20}$ −79·4° (*c*, 0·91 in dioxan) (Found: C, 70·7; H, 10·3; N, 4·3. $C_{19}H_{33}O_3N$ requires C, 70·5; H, 10·3; N, 4·3%).

The keto-ester (7 g.), sodium acetate (5 g.), and acetic anhydride (50 c.c.) were heated for 4 hr. under reflux. The mixture was evaporated under reduced pressure, treated with water, and extracted with ether. After the extract had been washed with aqueous sodium hydroxide and water, it was dried and evaporated, and the residue treated with Girard reagent T. The non-ketonic residue (3·4 g.), b. p. 185—190°/0·3 mm., consisted of *ester enol-acetate* (Found: C, 71·8; H, 10·2. $C_{22}H_{36}O_4$ requires C, 72·5; H, 10·0%) from which the corresponding *acid*, b. p. 165—170°/0·1 mm., was obtained by hydrolysis with methanolic N-potassium hydroxide (Found: C, 71·4; H, 9·7%; equiv., 334. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%; equiv., 350).

(ii) Methyl eperuate (25 g.) in refluxing acetone (300 c.c.) was oxidised by the gradual addition (Soxhlet) of potassium permanganate until reaction ceased (36 hr.). The precipitate was collected, the filtrate evaporated, and the residue shaken with a mixture of ether and water containing sulphur dioxide. Keto-ester (18 g.), b. p. 152°/0·2 mm., n_D^{16} 1·4940, was isolated from the ether layer; a small fraction of higher b. p. deposited solid which was separated by addition of methanol and consisted of hydroxy-ester (X; R = CO_2Me) (below), m. p. 184—185°.

The precipitate collected from the reaction mixture was stirred with warm water (100 c.c.) which was then filtered and acidified with sulphur dioxide. Hydrolysis of the ether-extracted product with boiling aqueous 2N-sodium hydroxide afforded an *acid*, which crystallised from ethyl acetate in needles (0·7 g.), m. p. 218—219° (Found: C, 67·4; H, 9·4. $C_{15}H_{24}O_4$ requires C, 67·2; H, 9·0%). The *dimethyl ester*, prepared by the action of diazomethane in ether, was a viscous liquid, b. p. 115°/0·1 mm. [Found: C, 69·0; H, 9·7%; *M* (Rast), 322. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%; *M*, 296].

Decahydro-6-hydroxy-5-(4-methoxycarbonyl-3-methylbutyl)-1 : 1 : 10-trimethylnaphthalene (VIII; R = Me, R′ = OH).—Ethereal solutions of the keto-ester (VII; R = Me) (4·5 g.) and of lithium aluminium hydride (0·72 g.) were heated together under reflux for 1 hr., and the product isolated after the addition of dilute hydrochloric acid gave the *hydroxy-ester* (VIII; R = Me, R′ = OH) as a colourless oil (2·8 g., 70%), b. p. 160—162°/0·1 mm., n_D^{16} 1·500 (Found: C, 74·2; H, 11·2. $C_{20}H_{36}O_3$ requires C, 74·0; H, 11·2%).

Cyclisation of the Keto-ester (VII; R = Me).—A solution of the keto-ester (10 g.) in toluene (100 c.c.) was gradually mixed with alcohol-free sodium methoxide (1·7 g.), and after 2 hr. at room temperature, was heated under reflux for 2 hr. After cooling, the product was treated

with ice-water, and the toluene solution separated, washed with aqueous sodium hydroxide, and evaporated. The residue of *methyl perhydro-14-hydroxy-1 : 1 : 7 : 12-tetramethylphenanthrene-8-carboxylate* (X; R = CO_2Me) crystallised from methanol in needles (2·4 g.), m. p. 184—185° (Found: C, 74·6; H, 10·3. $C_{20}H_{34}O_3$ requires C, 74·5; H, 10·6%). When the orange-yellow aqueous solution and alkali washings were acidified, a brownish oil was obtained which exhibited a strong, purple ferric reaction. It formed a chloroform-soluble copper complex, but the recovered carbonyl compound neither distilled nor gave crystalline derivatives.

The hydroxy-ester (0·3 g.) was heated with fused potassium hydrogen sulphate (1·5 g.) at 200—210° for ½ hr., and water and ether were added to the cooled product. The ether-soluble material gave when distilled (bath-temp. 130°/0·05 mm.) an *anhydro-ester*, n_D^{17} 1·5180. Light absorption in ethanol: 240 mμ (log ε 3·44) (Found: C, 78·7; H, 10·0. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Selenium Dehydrogenation of the Keto-ester (VII; R = Me).—Dehydrogenation of the ester (15 g.) with selenium (20 g.) at 300—340° for 45 hr. and ether-extraction of the product gave a brown gum which was decolorised by passing its solution in light petroleum through alumina, and then distilled. The first fraction (2·5 g.), b. p. <95°/0·05 mm., n_D^{17} 1·5158, contained incompletely dehydrogenated products and failed to give crystalline derivatives. The portion of b. p. 115—120°/0·05 mm. (3·5 g.) solidified and crystallised from methanol in plates, m. p. 83—84° undepressed by a specimen of pimanthrene (V; R = H) kindly provided by Professor R. D. Haworth, F.R.S. (Found: C, 92·8; H, 7·1. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). The picrate had m. p. 131—132° (lit., 132°) and the styphnate, m. p. 155·5° (lit., 159°). The intermediate fraction (4 g.), b. p. 96—115°/0·05 mm., was liquid, and a sample gave pimanthrene picrate (yield, *ca.* 90%) when mixed with alcoholic picric acid.

Dehydrogenation of the hydroxy-ester (VIII; R = Me, R′ = OH) (2·5 g.) under similar conditions to the above keto-ester (VII; R = Me) gave a yellow oil (1·3 g.) which after distillation was crystallised from methanol and had m. p. 82—83° alone or mixed with authentic pimanthrene. The trinitrobenzene derivative also was identical with the corresponding pimanthrene compound of m. p. 158°.

Dihydro-14-demethyleperuic Acid (VIII; R = R′ = H).—A mixture of the keto-ester (VII; R = Me) (10 g.), potassium hydroxide (7 g.), and 90% hydrazine hydrate (4 g.) in diethylene glycol (50 c.c.) was refluxed for 1½ hr., and then concentrated to b. p. 195° and further refluxed for 4 hr. The product was precipitated from the diluted ether-washed solution by acidification, and after being collected in ether was distilled. *Dihydro-14-demethyleperuic acid* (6·5 g., 71·5%), b. p. 168—170°/0·2 mm., slowly crystallised and had m. p. 38—40°, $[\alpha]_D^{18}$ −32° (*c*, 1·73) (Found: C, 76·9; H, 11·1%; equiv., 292. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·5%; equiv., 294·5). Its *p-bromophenacyl ester*, plates (from aqueous ethanol), had m. p. 68—69° (Found: C, 66·0; H, 8·1; Br, 16·0. $C_{27}H_{39}O_3Br$ requires C, 66·0; H, 8·0; Br, 16·3%).

Perhydro-14-hydroxy-8-hydroxymethyl-1 : 1 : 7 : 12-tetramethylphenanthrene (X; R = CH_2·OH). —The ester (X; R = CO_2Me) (0·5 g.), dissolved in ether–tetrahydrofuran (25 c.c. of 1 : 1 mixture), was heated under reflux with a solution of lithium aluminium hydride (0·5 g.) in ether for 1 hr. Treatment when cold with dilute hydrochloric acid and evaporation of the ether layer gave the *diol* (X; R = CH_2·OH) which crystallised from aqueous methanol as leaflets (0·39 g. 86%), m. p. 144—145° (Found: C, 77·2; H, 11·2. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·2%).

The diol (0·8 g.), dissolved in pyridine (8 c.c.), was oxidised overnight at room temperature with chromic anhydride–pyridine (Poos, Arth, Beyler, and Barrett, *J. Amer. Chem. Soc.*, 1953, **75**, 427). The mixture was filtered, and the filtrate treated with water and ether-extracted. The extracted solid crystallised from acetone in needles (0·65 g.), m. p. 250° (decomp.), consisting of the *hydroxy-acid* (X; R = CO_2H) (Found: C, 74·1; H, 10·7. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·5%) characterised by reaction with diazomethane to give the ester (X; R = CO_2Me), m. p. and mixed m. p. 184°. When the diol (0·65 g.) was heated under reflux with benzoquinone (2·4 g.) and aluminium *tert.*-butoxide (2·55 g.) in benzene, and the product remaining after acidification and steam-distillation chromatographed in benzene on alumina (20 g.), the principal fraction consisted of unchanged diol (0·45 g.), m. p. 144—145°, which was eluted with benzene–ether (1 : 1). A minute fore-run removed with benzene was uncrystallisable.

Selenium Dehydrogenation of Dihydro-14-demethyleperuic Acid (VIII; R = R′ = H).—Treatment of the acid (VIII; R = R′ = H) (8 g.) with selenium (10 g.) at 300—340° for 48 hr. yielded an oil which was dissolved in light petroleum and passed through alumina. The bulk of the eluate had b. p. 88—90°/0·2 mm., n_D^{20} 1·5148, and apparently consisted of 1 : 2 : 3 : 4-*tetrahydro*-1 : 1-*dimethyl*-5-*isopentylnaphthalene* (IX) (5·1 g.) (Found: C, 87·8; H, 11·5. $C_{17}H_{26}$ requires C, 88·6; H, 11·4%) which failed to give crystalline products with picric acid or trinitro-

benzene. Further treatment of the tetralin with selenium at 340—360° for 48 hr., or in a sealed tube at 310°, was without effect. Finally, dehydrogenation of the tetralin (1·7 g.) was carried out with selenium (2 g.) for 35 hr. at 355° (electric furnace) in a sealed tube. Two fractions were thus obtained of which that of b. p. 185°/15 mm., n_D^{21} 1·5185, appeared to be largely the original tetralin (0·45 g.). The portion of b. p. 155°/15 mm. (0·3 g.), n_D^{21} 1·5480, however, gave a *trinitrobenzene derivative*, yellow needles, m. p. 145—146°, from ethanol (Found: C, 59·9; H, 4·3; N, 11·3. $C_{13}H_{14}.C_6H_3O_6N_3$ requires C, 59·5; H, 4·5; N, 11·0%).

5-3'-Carboxybutyldecahydro-1 : 1 : 6 : 10-tetramethylnaphthalene (XII).—Methyl dihydroeperuate (30 g.) in ether (150 c.c.) was slowly added to Grignard reagent prepared from bromobenzene (34 g.) and magnesium (5 g.), and the mixture set aside overnight. The pasty mass was then heated under reflux for 1 hr. and the product worked up with ice and aqueous ammonium chloride. Unchanged ester was removed by heating with methanolic N-potassium hydroxide, and of the residue the portion dissolved after 2 hours' refluxing in acetic acid (100 c.c.), consisting of a viscous liquid (22 g.), b. p. 206—208°/0·03 mm., n_D^{18} 1·5520, was regarded as the diphenylethylene (XI).

A solution of this product (21 g.) in chloroform (20 c.c.) and acetic acid (150 c.c.) was treated below 30° with acetic acid (40 c.c.) and water (15 c.c.) containing chromic anhydride (25 g.). After being stirred for a further ½ hr., the solution was cooled to 5° and excess of reagent destroyed with sulphur dioxide. Treatment with water and concentration at reduced pressure on a steam-bath to remove acetic acid was followed by ether-extraction, the product being isolated from the extract with aqueous sodium carbonate. Acidification precipitated the *derivative* (XII) (12 g.), a viscous oil, b. p. 168—170°/0·2 mm., n_D^{17} 1·5010 (Found: C, 77·9; H, 11·4%; equiv., 294. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·6%; equiv., 294·5). The *p-bromophenacyl ester* crystallised in leaflets, m. p. 86—87°, from aqueous alcohol (Found: C, 66·0; H, 8·4. $C_{27}H_{39}O_3Br$ requires C, 66·0; H, 8·0%). In later preparations the acetic acid solution of crude product was oxidised without isolation of the phenylethylene, the yield of acid (XII) from (III; R = R' = Me) being 52%.

Decahydro-1 : 1 : 6 : 10-tetramethyl-5-3'-oxobutylnaphthalene (XIV).—The methyl ester (8·5 g.), b. p. 134—136°/0·2 mm., of (XII) and Grignard reagent from bromobenzene (8·6 g.), under conditions used for the preparation of the diphenylethylene (XI), gave the lower *homologue* (XIII), which crystallised from the reaction product as leaflets, m. p. 116°, $[\alpha]_D^{18}$ −24·4° (*c*, 2·5). Light absorption in chloroform: max. at 208, 244 mμ (log ε, 4·38, 4·17) (Found: C, 89·9; H, 10·0. $C_{31}H_{42}$ requires C, 89·8; H, 10·2%).

A solution of the hydrocarbon (XIII) (9 g.) in ethyl acetate (75 c.c.) was ozonised at 0° and then treated with water and zinc dust. After evaporation of the original solvent at room temperature the aqueous mixture was heated under reflux for 1 hr. and filtered, and the product isolated in ether. Traces of acidic material were removed with aqueous sodium carbonate, and the residue left after evaporation of the ether was treated with excess of Girard reagent T. The ketone (XIV) was thus obtained as a mobile liquid (*ca.* 3·7 g., 65%), b. p. 128°/0·05 mm., characterised by a *semicarbazone*, needles, m. p. 195°, from aqueous ethanol (Found: C, 71·4; H, 10·7; N, 12·8. $C_{19}H_{35}ON_3$ requires C, 71·0; H, 11·0; N, 13·1%).

5-2'-Carboxyethyldecahydro-1 : 1 : 6 : 10-tetramethylnaphthalene (XV).—The ketone (1·5 g.), dissolved in dioxan (60 c.c.) to which aqueous sodium hydroxide (12·5 c.c. of 10%) was added, was treated at 60° with iodine–potassium iodide solution until the mixture remained yellow for 5 min. It was then cooled, diluted with water (200 c.c.), filtered, treated with a small quantity of sodium hydrogen sulphite, and finally acidified. The gummy precipitate was taken up in ether, and the ethereal solution extracted with alkali to yield the *acid* (XV) which crystallised from aqueous methanol in needles, m. p. 134°, $[\alpha]_D^{17}$ −29·9° (*c*, 1·5) (Found: C, 76·3; H, 10·7%; equiv., 266. $C_{17}H_{30}O_2$ requires C, 76·6; H, 11·4%; equiv., 266·4).

5-(3 : 3-Diphenylprop-2-enyl)decahydro-1 : 1 : 6 : 10-tetramethylnaphthalene (XVI).—The product obtained from the methyl ester of (XV), b. p. 125° (bath-temp.)/0·1 mm. (1·3 g.), and phenylmagnesium bromide (from bromobenzene, 2·25 g., and magnesium, 0·35 g.) as in the preparation of (XI), was finally heated for 3 hr. in acetic acid (12 c.c.), and the soluble portion was isolated and eluted from alumina in light petroleum. Evaporation of the solution gave the *hydrocarbon* (XVI) (1·46 g.), crystallising from acetone in plates, m. p. 118—119°. Light absorption in hexane: max., 250 mμ (log ε 4·18) (Found: C, 89·9; H, 10·3. $C_{29}H_{38}$ requires C, 90·1; H, 9·9%).

A mixture of the diphenylethylene (XVI) (1·46 g.) and *N*-bromosuccinimide (0·73 g.) in carbon tetrachloride (30 c.c.) containing a trace of benzoyl peroxide was irradiated with ultraviolet light during 1 hour's refluxing. The filtered solution was treated with diethylaniline

(4 c.c.) and after evaporation of the carbon tetrachloride was heated to boiling for 10 min. Acidification and ether-extraction followed by purification in light petroleum on alumina (30 g.) led to the recovery of the colourless hydrocarbon (XVI) (0·93 g.), m. p. 115—116° undepressed by an authentic specimen.

Dehydrogenation of 5-2′-Carboxyethyldecahydro-1 : 1 : 6 : 10-tetramethylnaphthalene (XV).—The distillable product obtained by heating the acid (XV) (1·5 g.) with selenium (4·5 g.) for 40 hr. at 340—360° was a liquid (0·6 g.) (n_D^{19} 1·563) which yielded a picrate, orange needles, m. p. 83—84°, from methanol (Found: C, 57·6; H, 4·7; N, 10·5. $C_{14}H_{16}.C_6H_3O_7N_3$ requires C, 58·1; H, 4·6; N, 10·2%). Ruzicka, Ehmann, and Mörgeli (*Helv. Chim. Acta*, 1933, **16**, 268) record m. p. 82° for 1-ethyl-2 : 5-dimethylnaphthalene picrate but no analysis. The *trinitrobenzene compound* crystallised from ethanol in yellow needles, m. p. 118—119° (Found: C, 60·1; N, 10·7. $C_{14}H_{16}.C_6H_3O_6N_3$ requires C, 60·4; H, 4·8; N, 10·5%). A specimen synthesised from 2 : 5-dimethyl-1-tetralone had m. p. and mixed m. p. 118—119°.

2 : 5-*Dimethyl*-1-iso*pentylnaphthalene* (I; R = CH_2·CH_2·$CHMe_2$).—A solution of *iso*pentyl bromide (1·2 g.) in ether (5 c.c.) was mixed with lithium (0·25 g.) and ether, and the reaction controlled by ice-cooling. After being stirred for an hour the solution was filtered under nitrogen, mixed with 2 : 5-dimethyl-1-tetralone (1 g.), and heated under reflux for 1 hr. Next day water was added and the product contained in the ether was fractionated with Girard's reagent T. The non-ketonic portion (0·8 g.), distilled twice from sodium, was an oil, n_D^{17} 1·5508, which when dehydrogenated with selenium had n_D^{18} 1·5920, but failed to give homogeneous crystalline derivatives. The dihydronaphthalene (XVII) (1·1 g.) was then heated in boiling xylene (8 c.c.) with chloranil (1·4 g.) for 20 hr., the mixture afterwards being diluted with light petroleum, filtered, washed with sodium hydroxide and dithionite, dried, and distilled. The distillate (0·8 g.), b. p. 135° (bath-temp.)/0·05 mm., n_D^{22} 1·5642, of 2 : 5-dimethyl-1-*iso*pentylnaphthalene gave a *trinitrobenzene derivative* crystallising from ethanol in yellow needles, m. p. 91—92° (Found: C, 63·1; H, 5·7. $C_{17}H_{23}.C_6H_3O_6N_3$ requires C, 62·8; H, 5·7%).

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A Synthesis of (±)-Phellandral.

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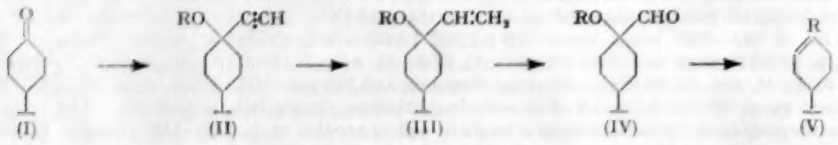
The synthesis of (±)-phellandral from dihydrocryptone has been achieved. Work on 1-vinyl*cyclo*hexanol as a model compound is also described.

THE terpene aldehyde (−)-phellandral occurs with (−)-phellandrene in various eucalyptus oils (Penfold, *J.*, 1922, **121**, 266; Berry, Macbeth, and Swanson, *J.*, 1937, 986), and the (+)-form of both the aldehyde and the hydrocarbon have been isolated from *Phellandrium aquaticum* (*idem*, *ibid.*, p. 1448). Extensive studies in these laboratories (*J.*, 1939, 1245; 1940, 808; 1946, 145) suggested the structure (V; R = CHO) for phellandral; and this was supported by a synthesis described by Frank, Berry, and Shotwell (*J. Amer. Chem. Soc.*, 1949, **71**, 3890). In this, dihydrocryptone (I) was converted into the acetate of the corresponding cyanohydrin, which by deacetoxylation and hydrolysis of the resultant nitrile (V; R = CN) gave phellandric acid and thence on reduction a low yield of phellandral. The synthesis is thought not to be unambiguous, as a high temperature (575—600°) was required for deacetoxylation, and the nitrile was assumed to have its unsaturation in the position αβ to the cyano-group: and during hydrolysis of the nitrile αβ–βγ shifting of the double bond occurred so that a mixture of the unsaturated acids was obtained. Work on the synthesis of phellandral according to the scheme below (Macbeth, Aust. and N.Z. Assoc. for Advancement of Science, Sydney, August, 1952) was therefore continued, and an unequivocal synthesis of the aldehyde is now presented.

As some difficulty was experienced at the ozonolysis stage (III ⟶ IV), exploratory work was carried out with the readily available 1-vinyl*cyclo*hexanol (Cook and Lawrence, *J.*, 1938, 58). Best results were obtained by using a slight excess of ozone at −75° in

ethyl acetate solution, but even under these conditions the ozonide sometimes decomposed before the subsequent hydrogenation, although the yield of hydroxy-aldehyde was not noticeably affected. An improvement in overall yield was effected by ozonisation of 1-vinyl*cyclo*hexyl acetate, obtained by reduction of the corresponding ethynyl compound.



(I) (II) (III) (IV) (V)

About equal amounts of the acetoxy-acid and acetoxy-aldehyde were obtained, but deacetoxylation of the latter under mild conditions could not be effected. Dehydration of the hydroxy-aldehyde was also difficult, boiling acetic anhydride, for example, giving the acetoxy-aldehyde. *cyclo*Hexene-1-aldehyde, however, was easily derived by decomposition of the 2 : 4-dinitrophenylhydrazones.

In the synthesis of phellandral the condensation of dihydrocryptone with acetylene was best carried out with sodium acetylide in liquid ammonia, and the resultant mixture was separated into the *cis*- and the *trans*-form by fractional crystallisation of the *p*-nitrobenzoates. The configurations were assigned on the basis of the Auwers–Skita rule, the ethynyl and *iso*propyl groups being regarded as similar. The *trans*-acetate was prepared under conditions which do not effect rearrangement (Rupe, Meisner, and Kambli, *Helv. Chim. Acta*, 1928, **11**, 449). Catalytic reduction gave the vinyl compound (III; R = Ac), ozonolysis of which gave a mixture of the acetoxy-acid and acetoxy-aldehyde. The latter resisted attempts at deacetoxylation at temperatures below 300°, but hydrolysis to the hydroxy-aldehyde could be carried out; the latter was more simply obtained by direct ozonolysis of (III; R = H). The hydroxy-aldehyde was very resistant to dehydration to phellandral; *e.g.*, unchanged material was recovered from heating with potassium hydrogen sulphate at 160°, and from hot 10% alcoholic sulphuric acid; and acetic anhydride gave the acetoxy-aldehyde. Phosphorus oxychloride in pyridine effected direct dehydration in rather poor yield, but the most satisfactory method of recovery of phellandral was by the action of 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid. Dehydration during the reaction resulted in the formation of the 2 : 4-dinitrophenylhydrazone of phellandral.

Methods for the recovery of ketones have been described using pyruvic acid and hydrobromic acid (Mattox and Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882; Djerassi, *ibid.*, 1949, **71**, 1003), or pyruvic acid and sodium acetate (Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393). The latter proved ineffective, but the former reacted under relatively mild conditions. Pyruvic acid alone was also satisfactory although a higher temperature was needed. The recovered (±)-phellandral was characterised by its physical constants, by preparation of the semicarbazone and *p*-nitrophenylhydrazone, and by oxidation to phellandric acid.

Experimental

Dihydrocryptone.—This was prepared from cryptone isolated from *Eucalyptus cneorifolia* by reduction in the presence of palladium–charcoal. The product was shaken with disodium sulphite and then with 35% aqueous sodium hydrogen sulphite. From the latter, dihydrocryptone was obtained by decomposition with aqueous sodium carbonate and isolation with ether.

cis- *and* trans-1-*Ethynyl*-4-iso*propyl*cyclo*hexanol.*—(*a*) Potassium *tert.*-pentyloxide, prepared from potassium (5 g.), was treated with dihydrocryptone (17·5 g.), and the solution cooled and added dropwise during 30 min. to a saturated solution of acetylene in ether (50 ml.) at −15°. Acetylene was passed into the mixture for a further 10 min., the product decomposed with ammonium chloride, and the ether separated and washed with 35% sodium hydrogen sulphite and then water. The ethereal residue yielded the mixture of ethynyl compounds, b. p. 68°/0·4 mm.

(*b*) The procedure detailed by Vogel ("Practical Organic Chemistry," 2nd edn., 1951, Longmans, p. 1002) for the preparation of 1-ethynyl*cyclo*hexanol employing sodium acetylide in liquid ammonia was used. The residue left after decomposition with ammonium chloride and evaporation of the ammonia was extracted (Soxhlet) with ether, and the extract washed with water and dilute acid, and evaporated. Distillation gave the mixture, b. p. 83°/3 mm., which partly crystallised, yielding about equal amounts of an oil and the solid trans-*compound*. Crystallisation of the latter from light petroleum (b. p. <40°) gave long needles, m. p. 45° (Found: C, 79·6; H, 11·1. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%). The trans-*acetate* prepared with boiling acetic anhydride crystallised from light petroleum (b. p. <40°) as large prisms, m. p. 44° (Found: C, 75·4; H, 9·8. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%). The acetate was recovered unchanged after 1 hour's refluxing with 15% aqueous potassium hydroxide but was hydrolysed by 2 hours' refluxing with 20% aqueous methanolic potassium hydroxide. The trans-p-*nitrobenzoate*, prepared by means of the acid chloride in boiling benzene and a trace of pyridine for 6 hr., crystallised from methanol as cream-coloured rhombs, m. p. 82—83° (Found: C, 68·5; H, 6·4; N, 4·5. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·4%), hydrolysed in 2 hr. with 10% methanolic potassium hydroxide. Similar esterification of the liquid portion and fractional crystallisation gave a further crop of the *trans*-derivative and the cis-*ester* in the ratio 3 : 1. Crystallisation of the latter from methanol gave plates, m. p. 120—121° (Found: C, 68·8; H, 6·2; N, 4·6. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·4%). Hydrolysis of this ester with methanolic potassium hydroxide, isolation with ether, and distillation gave cis-1-*ethynyl*-4-iso*propyl*cyclo*hexanol*, b. p. 94°/7 mm., n_D^{25} 1·4720, d_4^{25} 0·9182, $[R_L]_D^{25}$ 50·7 (Calc.: 50·5) (Found: C, 79·3; H, 10·9. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%).

trans-4-iso*Propyl*-1-*vinyl*cyclo*hexanol*.—The *trans*-ethynyl compound (10 g.) in alcohol (100 ml.) was hydrogenated at room temperature and pressure in the presence of a 10% palladium–calcium carbonate catalyst (1 g.), until 1·35 l. (1 mol.) of hydrogen were absorbed, whereupon reduction slackened noticeably. Temperature control was obtained by using a flask with a sealed-in cooling coil. The catalyst was separated, and the filtrate diluted with water and extracted with ether. Evaporation of the dried extract and distillation of the residue gave an oil, b. p. 79—80°/2 mm., which gradually solidified. Crystallisation from light petroleum (b. p. <40°) gave needles, m. p. 21° (Found: C, 77·7; H, 11·9. Calc. for $C_{11}H_{20}O$: C, 78·6; H, 11·9%). The acetate, prepared similarly from *trans*-4-*iso*propyl-1-vinyl-*cyclo*hexanyl acetate, was obtained as an odourless oil, b. p. 91—92°/2 mm. The p-*nitrobenzoate*, prepared in benzene, crystallised from methanol as cream-coloured needles, m. p. 73° (Found: C, 68·1; H, 7·2; N, 4·6. $C_{18}H_{23}O_4N$ requires C, 68·1; H, 7·3; N, 4·4%). The cis-p-*nitrobenzoate*, obtained by esterification and fractional crystallisation from the partial reduction product of the mixed ethynyl compounds, crystallised from methanol as cream-coloured needles, m. p. 103° (Found: C, 68·3; H, 7·3; N, 4·7%).

Ozonolyses.—The apparatus employed was a ten-tube Towers ozoniser fitted with a flow-meter and calibrated at a rate of 200 c.c. of oxygen per min. Equilibrium was established after 3 hours' operation.

1-*Hydroxy*cyclo*hexanealdehyde*.—1-Vinyl*cyclo*hexanol (12 g.) in ethyl acetate (120 ml.) was cooled to −75° and treated with a 5% excess of ozone. The solution was then hydrogenated by use of a palladium–calcium carbonate catalyst in a flask held at 0° by a cooling coil. Reduction was variable and in some cases was not observed although the same products were obtained in all cases. Evaporation of the ethyl acetate yielded an oil which was washed with 10% sodium carbonate solution (A) and extracted with ether, and the ethereal solution shaken with saturated sodium hydrogen sulphite during 2 days. The precipitate (6·5 g.) was decomposed with 10% sodium carbonate solution, and the resultant oil (3 g.) isolated with ether and combined with a further fraction (1 g.) derived from the bisulphite liquors. After prolonged standing partial crystallisation occurred. Recrystallisation from hexane gave the *aldehyde* as prisms (0·5 g.), m. p. 84° (Found: C, 65·6; H, 9·4. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). Attempts to prepare a 2 : 4-dinitrophenylhydrazone (in alcoholic sulphuric acid) resulted in dehydration with formation of the derivative of *cyclo*hexene-1-aldehyde, m. p. 215° alone or mixed with an authentic sample (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737). The sodium carbonate washings (A) were made acid and extracted with ether. The ethereal residue crystallised from benzene–hexane to give 1-hydroxy*cyclo*hexanecarboxylic acid, m. p. 108° alone or mixed with an authentic sample (Bucherer, *Ber.*, 1894, **27**, 1231).

1-*Acetoxy*cyclo*hexanealdehyde*.—Similar ozonolysis of 1-acetoxyvinyl*cyclo*hexane (12 g.) yielded 1-*acetoxy*cyclo*hexanecarboxylic acid* (4 g.), which crystallised from hexane in plates, m. p. 103° (Found: C, 58·2; H, 7·4. $C_9H_{14}O_4$ requires C, 58·1; H, 7·5%). Alkaline

hydrolysis yielded the hydroxy-acid, m. p. and mixed m. p. 108°. The neutral fraction from the ozonolysis was distilled. The fraction, b. p. 80°/2·5 mm. (3 g.), consisted almost entirely of the acetoxy-aldehyde, as shown by the preparation of the 2 : 4-*dinitrophenylhydrazone* in high yield in acetic acid solution. Crystallisation from alcohol–ethyl acetate gave yellow plates, m. p. 158° (Found : C, 51·7; H, 5·2; N, 15·7. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·1; N, 16·0%). The *semicarbazone* formed needles (from alcohol), m. p. 193° (Found : C, 53·3; H, 7·4; N, 18·9. $C_{16}H_{17}O_3N_3$ requires C, 52·9; H, 7·5; N, 18·5%). Attempted deacetoxylation of the acetoxy-aldehyde by 1 hour's refluxing (bath-temp. 300°) under nitrogen resulted in recovery of the starting material. However, *cyclo*hexene-1-aldehyde was obtained as its 2 : 4-dinitrophenylhydrazone from attempts to prepare the derivative from the acetoxy-aldehyde in alcoholic solution with sulphuric acid. Similar ozonolysis of 1-acetoxy-4-*iso*propyl-1-vinyl*cyclo*hexane (9 g.) gave the *acetoxy-acid* (4 g.), which crystallised from hexane as prisms, m. p. 107° (Found : C, 63·3; H, 8·5. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The neutral fraction (3·0 g.) consisted mainly of the acetoxy-aldehyde. The 2 : 4-*dinitrophenylhydrazone*, prepared in acetic acid, crystallised from alcohol–ethyl acetate in yellow needles, m. p. 202—204° (Found : C, 55·0; H, 6·2; N, 14·0. $C_{18}H_{24}O_8N_4$ requires C, 55·1; H, 6·1; N, 14·3%). The *semicarbazone* crystallised from ethyl acetate as needles, m. p. 198° (Found : C, 58·4; H, 8·6; N, 15·8. $C_{13}H_{23}O_3N_3$ requires C, 58·0; H, 8·6; N, 15·6%). All attempts to eliminate elements of acetic acid from the acetoxy-aldehyde failed, although preparation of the 2 : 4-dinitrophenylhydrazone in the presence of alcoholic sulphuric acid yielded the derivative of phellandral.

1-*Hydroxy*-4-iso*propyl*cyclo*hexanealdehyde.*—Ozonolysis of the corresponding vinyl compound (10 g.) gave an *acid* fraction (0·5 g.) which formed a sparingly soluble sodium salt and crystallised from benzene–hexane as plates, m. p. 195°, alone or mixed with a sample derived from the acetate (Found : C, 64·6; H, 9·8. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). The neutral portion was shaken with saturated sodium hydrogen sulphite solution and left overnight. The precipitate was separated and decomposed with boiling 10% sodium carbonate solution. Isolation with ether gave a viscous oil which partly crystallised. Adherent oil was removed by solution in light petroleum (b. p. <40°) and filtration of the residue. Slow evaporation of the filtrate yielded further crops. Crystallisation from aqueous alcohol gave a micro-crystalline *aldehyde* (2·4 g.). The m. p. varied from 70° to 150°. Different samples showed the same analysis [Found : C, 70·5; H, 10·4%; *M* (Rast), 160. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%; *M*, 170]. The 2 : 4-*dinitrophenylhydrazone*, prepared in methyl alcohol containing 2% of sulphuric acid, crystallised from benzene–methanol as yellow needles, m. p. 184° (Found : C, 56·4; H, 6·6; N, 15·6. $C_{16}H_{22}O_6N_4$ requires C, 54·9; H, 6·3; N, 16·0%). This 2 : 4-dinitrophenylhydrazone underwent dehydration in hot alcoholic solution containing sulphuric acid (10%), yielding (±)-phellandral 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 198° (Found : C, 57·9; H, 5·9; N, 16·8. Calc. for $C_{16}H_{20}O_4N_4$: C, 57·9; H, 6·0; N, 16·9%). The hydroxy-aldehyde was recovered as the acetate after 2 hours' refluxing with acetic acid or acetic anhydride, and unchanged after 1 hour's boiling with 10% alcoholic sulphuric acid or heating for the same period with potassium hydrogen sulphate at 160°.

(±)-*Phellandral.*—(*a*) Direct formation of phellandral from the hydroxy-aldehyde (0·3 g.) was effected in low yield on treatment with redistilled phosphorus oxychloride (0·2 g.) at room temperature for 24 hr. Decomposition with ice and isolation with ether gave an oil, one half of which yielded the 2 : 4-dinitrophenylhydrazone (0·08 g.), m. p. and mixed m. p. 198°. The other portion was identified as its semicarbazone, m. p. and mixed m. p. 200°.

(*b*) Phellandral 2 : 4-dinitrophenylhydrazone (1 g.), derived from the hydroxy-aldehyde as above, was recovered unchanged after 48 hr. at room temperature in acetone (200 ml.) and hydrochloric acid (10 ml.). The 2 : 4-dinitrophenylhydrazone (0·5 g.) was also undecomposed after 3 hours' refluxing in chloroform (15 ml.) containing acetic acid (9 ml.), sodium acetate (0·23 g.), pyruvic acid (9 ml.), and water (3 ml.), during which period pyruvic acid (3 ml.) and water (2 ml.) were added in three portions. Recovery of (±)-phellandral from the phenylhydrazone was, however, effected by acting on it (5 g.) in chloroform (100 ml.) with pyruvic acid (100 ml.; B.D.H.) and hydrochloric acid in acetic acid (5 ml.; 4N) under reflux in nitrogen for 10 min. Dilution with water and chloroform and washing the latter with aqueous potassium carbonate gave on evaporation an oil which had b. p. 70°/1 mm. (1·4 g.), n_D^{16} 1·4880, n_D^{20} 1·4898, d_4^{18} 0·9430. This was identified as (±)-phellandral by preparation of its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 198°, and its *p*-nitrophenylhydrazone, m. p. and mixed m. p. 163—164° (Found : C, 66·9; H, 7·8; N, 14·7. Calc. for $C_{16}H_{21}O_2N_3$: C, 66·9; H, 7·4, N; 14·6%). The semicarbazone had m. p. and mixed m. p. 200° (Found :

C, 63·6; H, 9·2; N, 19·7. Calc. for $C_{11}H_{19}ON_3$: C, 63·2; H, 9·2; N, 20·1%). Oxidation with silver oxide (Burger and Macbeth, *loc. cit.*) yielded (±)-phellandric acid, m. p. and mixed m. p. 143—144°. Phellandral (0·8 g.) was also recovered in about 85% yield from its dinitrophenylhydrazone (2 g.) by heating it in pyruvic acid (50 ml.; B.D.H.) at 100° in nitrogen for 4 hr. and isolation with chloroform.

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The Infrared Spectra of Some Sulphonamides.

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The infrared spectra of various unsubstituted and *N*-substituted sulphonamides have been measured, and characteristic frequencies for the $SO_2{\cdot}NRR'$ group are discussed. From intensity measurements on the N–H bands at various concentrations, association constants have been obtained for solutions of several *N*-monosubstituted sulphonamides. The structure of the molecular compound prepared by Baxter, Cymerman-Craig, and Gilbert (*J.*, 1953, 2400) has been clarified by means of infrared measurements.

ALTHOUGH fairly detailed studies have been made of the infra-red spectra of the carboxyamides (Richards and Thompson, *J.*, **1947**, 1248; Lenormant, *Ann. Chim.*, 1950, **5**, 459; Davies and Hallam, *Trans. Faraday Soc.*, 1951, **47**, 1170; Letaw and Gropp, *J. Chem. Phys.*, 1953, **21**, 1621; Gierer, *Z. Naturforsch.*, 1953, **8**, *B*, 644, 654) little discussion of the sulphonamides has appeared. A few isolated observations have been made on the infra-red and Raman spectra of benzene- and toluene-sulphonamides (Schreiber, *Analyt. Chem.*, 1949, **21**, 1168; Angus, Leckie, and Williams, *Trans. Faraday Soc.*, 1938, **34**, 793) but these were not primarily concerned with the spectroscopy of the $SO_2{\cdot}NH_2$ group as such. Adams and Tjepkema (*J. Amer. Chem. Soc.*, 1948, **70**, 4204) found a strong band in the infra-red spectra of several *NN*-disubstituted sulphonamides at 1160—1180 cm.$^{-1}$ which could be assigned to the sulphonyl group.

TABLE 1.

No.	Compound	No.	Compound
1	2-*N*-*p*-Diphenylylaminoethanol	13	*N*-Benzenesulphonyl-*p*-phenetidine
2	*N*-*p*-Diphenylyltoluene-*p*-sulphonamide + *N*-*p*-Diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide	14	*N*-Benzenesulphonyl-*p*-nitroaniline
3	*N*-*p*-Diphenylylethylamine	15	*N*-Methyl-*p*-acetamidobenzenesulphonanilide *
4	*N*-*p*-Diphenylyl-*N*-ethyltoluene-*p*-sulphonamide *	16	*NN*-Diethyltoluene-*p*-sulphonamide
5	*N*-*p*-Diphenylyl-2-methoxyethylamine *	17	Methanesulphonanilide
6	*N*-*p*-Diphenylyl-*N*-2′-methoxyethyltoluene-*p*-sulphonamide *	18	Methanesulphonamide
7	*N*-*p*-Diphenylyltoluene-*p*-sulphonamide	19	*N*-Methylmethanesulphonamide *
8	Benzenesulphonamide	20	*N*-Ethyltoluene-*p*-sulphonamide
9	Toluene-*p*-sulphonamide	21	*N*-*p*-Diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide *
10	Benzenesulphonanilide	22	2-Anilinoethanol
11	Sulphanilamide	23	*N*-Phenyl-*N*-*n*-propylaminoethanol *
12	*o*-Sulphobenzoimide (saccharin)	24	Acetanilide
		25	Diphenylamine

* See Experimental.

In the present work the spectra of the 25 compounds listed in Table 1 have been measured between 400 and 4000 cm.$^{-1}$ both in the solid state and, over the 1100—1400 cm.$^{-1}$ and 2700—4000 cm.$^{-1}$ regions, in solution. The principal results are summarised in Table 2, where compounds are classified as unsubstituted, *N*-monosubstituted, and *NN*-disubstituted sulphonamides. The spectroscopic method is then applied to the solution of the structure of the molecular compound (No. 2) formed between *N*-*p*-diphenylyltoluene-*p*-sulphon-

amide (No. 7) and *N*-*p*-diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide (Baxter, Cymerman-Craig, and Gilbert, *loc. cit.*).

Experimental

Source of Materials.—Compounds 1, 2, and 3 were the pure samples described by Baxter, Cymerman-Craig, and Gilbert (*loc. cit.*). Nos. 7—14, 16—18, 20, 24, and 25 had the m. p.s recorded in the literature. 2-Anilinoethanol (No. 22) had b. p. 103—104°/0·01 mm., n_D^{24} 1·5755.

Compound 4 was unchanged after 38 hours' boiling with 24% aqueous or alcoholic hydrochloric acid, or after 6 hours' refluxing with alcoholic potassium hydroxide, and was hydrolysed to No. 3 only by concentrated sulphuric acid. Similarly, hydrolysis of No. 6 could be effected only by concentrated sulphuric acid, which gave equal quantities of compounds 1 and 5 in low yield. Attempted reaction of 2-methoxyethyltoluene-*p*-sulphonate and 4-acetamidodiphenyl failed. Reaction of 4-aminodiphenyl and methoxyacetic acid gave 4-methoxyacetamidodiphenyl, readily reduced by lithium aluminium hydride to compound 5 in excellent yield. Compound 21 was prepared by reaction of toluene-*p*-sulphonyl chloride with No. 1, and an equimolecular mixture of compounds 21 and 7 yielded the molecular compound (No. 2) previously described.

Alkylation of *N*-*n*-propylaniline with 2-bromoethanol gave *N*-phenyl-*N*-*n*-propylaminoethanol (No. 23), previously prepared by a different route (Bergmann, Lavie, and Pinchas, *J. Amer. Chem. Soc.*, 1951, **73**, 5662).

N-*Methylmethanesulphonamide*.—A solution of methanesulphonyl chloride (11·45 g., 0·1 mole; b. p. 99°/35 mm.; $n_D^{21\cdot5}$ 1·4522) in dry ether was added gradually to ethereal methylamine (0·3 mole) at 0°. When the exothermic reaction had subsided, the mixture was kept at room temperature for 1 hr. and the precipitate filtered off and washed with ether and chloroform (methylammonium chloride; 5·95 g., 88%). Distillation of the filtrate gave the sulphonamide (9·8 g., 90%) as a hygroscopic oil, b. p. 117—118°/0·3 mm., n_D^{23} 1·4508, miscible with cold water (Found : C, 21·95; H, 6·45. Calc. for $C_2H_7O_2NS$: C, 22·0; H, 6·45%). Helferich and Grunert (*Ber.*, 1940, **73**, 1131) give b. p. 118°/0·3 mm., and 60% yield.

N-p-*Diphenylyl*-N-*ethyltoluene*-p-*sulphonamide*.—A mixture of *N*-*p*-diphenylyltoluene-*p*-sulphonamide (16·16 g.), sodium ethoxide (from sodium, 1·15 g.) and ethyl iodide (4·3 c.c.) in alcohol (500 c.c.) was refluxed for 10 hr. On cooling, the clear solution deposited the above *sulphonamide* (11·77 g., 67%), crystallising from alcohol as needles, m. p. 120·5—121° (Found : C, 71·55; H, 6·1. $C_{21}H_{21}O_2NS$ requires C, 71·75; H, 6·0%). The residue left on evaporation of the mother-liquors was separated by sodium hydroxide (0·5N) into (i) a further 1·6 g. (9·5%) of product (m. p. 117—118°) and (ii) starting material (2·7 g., 17%), m. p. 152—154°.

Hydrolysis. The preceding sulphonamide (3·04 g.) was refluxed with sulphuric acid (100 c.c.; 14N) for 21 hr. Dilution with water (100 c.c.) precipitated starting material (1·45 g., 47·5%), m. p. 117·5—119°. The aqueous filtrate was basified and extracted with ether. The dried (Na_2SO_4) extracts afforded *N*-*p*-diphenylylethylamine (0·65 g., 38%), m. p. 68—69° (Baxter, Cymerman-Craig, and Gilbert, *loc. cit.*, give m. p. 67—69°).

N-p-*Diphenylyl*-N-2′-*methoxyethyltoluene*-p-*sulphonamide*.—(*a*) A mixture of *N*-*p*-diphenylyltoluene-*p*-sulphonamide (18·64 g.), 2-methoxyethyl bromide (6·2 c.c., 10% excess), and anhydrous potassium carbonate (4·4 g., 10% excess) in dry acetone (350 c.c.) was refluxed for 26·5 hr. The residue left on evaporation of the solvent was extracted with boiling sodium hydroxide solution (400 c.c.; 0·5%), and acidification of the filtrate gave starting material (6·35 g., 34%). The water-insoluble portion crystallised from alcohol or light petroleum (b. p. 60—90°) as needles, m. p. 99·5—100·5°, of N-p-*diphenylyl*-N-2′-*methoxyethyltoluene*-p-*sulphonamide* (8·17 g., 37%) (Found : C, 68·95, 69·0; H, 5·9, 6·1; O, 12·4; N, 4·05. $C_{22}H_{23}O_3NS$ requires C, 69·25; H, 6·05; O, 12·6; N, 3·7%).

(*b*) Reaction of *N*-*p*-diphenylyl-2-methoxyethylamine and toluene-*p*-sulphonyl chloride in pyridine at 90° for 2 hr. gave prisms, m. p. 100—100·5° (from alcohol), undepressed on admixture with the material prepared as in (*a*).

Hydrolysis. The preceding sulphonamide (3·8 g.) was refluxed with hydrochloric acid (90 c.c.; 24% w/v) for 19 hr. The hot solution was filtered, and the residue extracted with boiling water, leaving starting material (2 g., 52%; m. p. and mixed m. p. 98—99°). The combined filtrates were basified and extracted with ether. Evaporation of the dried extracts and crystallisation of the residue from light petroleum gave 2 fractions : (i) 2-*N*-*p*-diphenylylaminoethanol (0·3 g., 14%), m. p. and mixed m. p. 111—112°; (ii) *N*-*p*-diphenylyl-2-methoxyethyl-

amine (0·25 g., 13%), m. p. 54—57°, undepressed on admixture with the pure material (m. p. 59·5—60·5°) described below.

4-Methoxyacetamidodiphenyl.—A mixture of 4-aminodiphenyl (28 g.) and methoxyacetic acid (14·9 g.; Rothstein, *Bull. Soc. chim.*, 1932, **51**, 839) was heated for 2 hr. at 150—160°. Water distilled off, and the cooled melt crystallised from alcohol as plates (31·7 g., 79%) of *4-methoxyacetamidodiphenyl*, m. p. 142·5—143° (Found: C, 74·85; H, 6·6. $C_{15}H_{15}O_2N$ requires C, 74·65; H, 6·3%).

N-p-*Diphenylyl-2-methoxyethylamine.*—Powdered 4-methoxyacetamidodiphenyl (23·35 g.) was placed in the thimble of a Soxhlet extractor and refluxed with a solution of lithium aluminium hydride (3·7 g.) in ether (400 c.c.) for 17·5 hr.; unchanged amide (3·3 g.; m. p. 143°) remained in the thimble. The complex was decomposed with water and extracted with ether, giving N-p-*diphenylyl-2-methoxyethylamine* (17·6 g., 92% calc. on amide changed), needles, m. p. 59·5—60·5° (Found: C, 79·25; H, 7·45; N, 6·25. $C_{15}H_{17}ON$ requires C, 79·25; H, 7·55; N, 6·15%), from light petroleum.

N-p-*Diphenylyl-N-2′-hydroxyethyltoluene-p-sulphonamide.*—Reaction of toluene-*p*-sulphonyl chloride and 2-*N-p*-diphenylylaminoethanol in dry pyridine at 100° for 0·5 hr. gave needles (90% yield) of N-p-*diphenylyl-N-2′-hydroxyethyltoluene-p-sulphonamide*, m. p. 125—126° (Found: C, 68·7; H, 5·8; O, 13·1; S, 8·3. $C_{21}H_{21}O_3NS$ requires C, 68·65; H, 5·7; O, 13·1; S, 8·7%), from aqueous methanol.

N-*Methyl*-p-*acetamidobenzenesulphonanilide.*—A mixture of *p*-acetamidobenzenesulphonyl chloride and excess of *N*-methylaniline was heated at 100° for 10 min., giving N-*methyl*-p-*acetamidobenzenesulphonanilide* as plates (from alcohol), m. p. 152·5—153° (Found: C, 59·7; H, 5·6; N, 8·9. $C_{15}H_{16}O_3N_2S$ requires C, 59·25; H, 5·25; N, 9·2%).

N-*Phenyl*-N-*n-propylaminoethanol.*—A mixture of *N-n*-propylaniline (5·4 g.; n_D^{24} 1·5390) and 2-bromoethanol (5 g.) was heated at 150° for 1·5 hr., poured into water, and basified with sodium hydroxide. Extraction with ether and distillation of the dried (Na_2SO_4) extracts, finally through a 10 cm.-long Vigreux column, gave (i) unchanged *N-n*-propylaniline, b. p. 66—76°/0·001 mm., n_D^{25} 1·5339 (0·5 g., 9%), and (ii) *N*-phenyl-*N-n*-propylaminoethanol, b. p. 87—89°/0·001 mm., n_D^{25} 1·5507 (4·5 g., 64%) (Found: C, 73·15; H, 9·5; N, 7·55. Calc. for $C_{11}H_{17}ON$: C, 73·6; H, 9·5; N, 7·8%). Bergmann, Lavie, and Pinchas (*J. Amer. Chem. Soc.*, 1951, **73**, 5662) give b. p. 131°/3 mm., n_D^{21} 1·5470.

Spectroscopic Technique.—The infra-red spectra were measured with a Perkin-Elmer Model 12C spectrometer, converted into a double-pass instrument by Walsh's method (*J. Opt. Soc. Amer.*, 1952, **42**, 96), and using optics of potassium bromide for the region 400—700 cm.$^{-1}$, sodium chloride for 700—1400 cm.$^{-1}$, and calcium fluoride for 1400—4000 cm.$^{-1}$.

Solid specimens were measured either as vacuum-sublimed layers or as mulls in "Nujol." Sometimes slight differences were noted in the low-frequency region of the spectrum of the same substance measured by the two different methods, and in such cases the spectrum in "Nujol" was accepted as being the more reliable.

Solutions in methyl cyanide, carbon tetrachloride, carbon disulphide, and chloroform were measured in cells ranging from 0·05 cm. to 4 cm. in length. The solvents used were of "AnalaR" quality and were not further purified but were dried with silica gel before use. The 2% of ethanol used as a stabiliser in the "AnalaR" chloroform was removed immediately before use by repeated shaking with silica gel.

Results and Discussion

Characteristic Vibrations of the Sulphonyl Group.—As with the sulphones (Barnard, Fabian, and Koch, *J.*, 1949, **2442**) and the thiolsulphonates (Cymerman and Willis, *J.*, 1951, 1332) the sulphonamides all show two strong bands at frequencies near 1160 and 1350 cm.$^{-1}$ which leave no doubt that they are due to the symmetric and antisymmetric vibrations of the two S–O bonds, corresponding to the ν_1 and ν_3 vibrations of the SO_2 molecule (see Table 2). Both frequencies, and particularly the higher one, are somewhat greater than for the sulphones, which have their frequencies at 1130—1164 and 1312—1336 cm.$^{-1}$ in carbon tetrachloride and at 1124—1150 and 1299—1313 cm.$^{-1}$ in the solid state (Barnard, Fabian, and Koch, *loc. cit.*). They are, however, lower than the corresponding frequencies for the sulphonyl chlorides (1168—1183, 1361—1384 cm.$^{-1}$) or sulphonyl fluorides (1167—1197, 1401—1412 cm.$^{-1}$) as found in the Raman spectra of the liquids by Ham and Hambly (*Australian J. Chem.*, 1953, **6**, 135).

The lower frequency, at 1155—1170 cm.$^{-1}$, is little affected by the change from solid to solution, but the higher frequency is 10—20 cm.$^{-1}$ higher in carbon tetrachloride or carbon disulphide solution than in chloroform or in the solid state. Barnard, Fabian, and Koch also found in the sulphones a greater change in the higher than in the lower frequency on going from solid to solution, and explained this by pointing out that the higher frequency corresponds to the antisymmetric vibration, which has a more purely bond-stretching character than does the symmetric one, and is thus more strongly affected by intermolecular forces.

Both frequencies, and particularly the higher one, show slight increases on passage from the unsubstituted through the mono- to the di-substituted sulphonamides. Substitution by aromatic groups, as far as can be judged from the compounds studied, causes a greater increase than substitution by aliphatic groups. It is shown later that the *N*-mono-substituted sulphonamides are strongly associated in carbon tetrachloride solution, but less so in chloroform, while the *NN*-disubstituted compounds are known from the work of Chaplin and Hunter (*J.*, 1937, 1114) and Le Fèvre and Vine (*J.*, 1938, 1790) to be practically non-associated. Since association tends to reduce the frequency of the S–O vibrations, it is understandable that the frequencies of the *NN*-disubstituted sulphonamides are about 20 cm.$^{-1}$ higher than those of the other compounds in carbon tetrachloride and carbon disulphide solution but only about 10 cm.$^{-1}$ higher in chloroform or in the solid state.

A peculiar anomaly is found with methanesulphonamide in carbon disulphide solution, where the lower frequency occurs at 1215 instead of 1160 cm.$^{-1}$.

o-Sulphobenzoimide (saccharin) shows its higher frequency at a value somewhat above those for the other *N*-monosubstituted sulphonamides. This is probably due to ring strain, and analogous cases are found in the abnormally high carbonyl frequencies of *cyclo*pentanone (Hartwell, Richards, and Thompson, *J.*, 1948, 1436) and γ-butyrolactone (Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073).

Sulphanilamide was completely insoluble in any of the solvents used except methyl cyanide. Both the S–O vibrations are 10 cm.$^{-1}$ lower than for benzenesulphonamide in the same solvent. Kumler and Halverstadt (*J. Amer. Chem. Soc.*, 1941, **63**, 2182) have suggested, on the basis of dipole-moment data, that the structure of sulphanilamide contains a contribution from the form (I). The infra-red measurements support this view, since the S–O bonds in this structure, having more single-bond character than in the conventional formula, should have lower vibration frequencies.

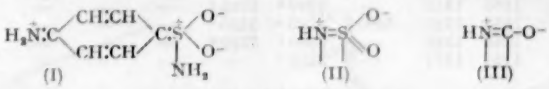
The third fundamental of the sulphur dioxide molecule, *viz.*, the symmetrical deformation vibration ν_2, occurs at 519 cm.$^{-1}$, and a search was made for a characteristic band in this region in the spectra of the sulphonamides. In the simplest compounds, methane- and *N*-methylmethane-sulphonamide, a strong band is readily discernible at 525—526 cm.$^{-1}$. In the more complex molecules there is usually more than one band in the 500—600 cm.$^{-1}$ region, but in every case a strong band, which may reasonably be attributed to this vibration, occurs between 520 and 550 cm.$^{-1}$. The fact that the frequency is always higher than in the sulphur dioxide molecule itself is to be attributed to the strong intermolecular bonding which must exist between adjacent molecules in the solid state and which will raise the frequency of the $-SO_2-$ deformation vibration (cf. Herzberg, "Infra-red and Raman Spectra," Van Nostrand, New York, 1945, p. 535).

Characteristic Vibration Frequency of the S–N *Bond.*—From a study of the Raman spectra of five compounds of different types containing the S–N linkage, Angus, Leckie, and Williams (*loc. cit.*) concluded that this bond has a characteristic stretching frequency at about 1070 cm.$^{-1}$. Almost all the sulphonamides measured during the present investigation show at least one strong absorption band between 1070 and 1100 cm.$^{-1}$, usually near 1090 cm.$^{-1}$, which may tentatively be identified with the S–N frequency. This assignment must be accepted with caution, however, for the following reasons: (*a*) Methanesulphonamide has no absorption between 990 and 1140 cm.$^{-1}$; (*b*) monosubstituted benzene rings, which occur in many of the compounds, are known to absorb weakly in this region (Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397); and (*c*) recent work by Hoffmann and Andress (*Naturwiss.*, 1954, **4**, 94) indicates that the S–N frequency may be as low as 550 cm.$^{-1}$.

Deformation Frequencies of the Amino- and Imino-groups.—There is still no general

agreement on the assignment of characteristic frequencies to the deformation vibrations of these groups in amides (Sutherland, *Adv. in Protein Chem.*, 1952, **7**, 291), on account of the interaction of the vibrations with the stretching vibration of the C–N bond, which occurs at an abnormally high frequency owing to the partial double-bond character of this bond in amides (Fraser and Price, *Nature*, 1952, **170**, 490). From the work of Barnard, Fabian, and Koch (*loc. cit.*) it seems that the sulphonyl group, having a different geometry from the carbonyl group, cannot readily take part in conjugative shifts within the molecule, so it is unlikely that the form (II) plays such an important part in determining the structure of the sulphonamides as its counterpart (III) does with the amides. It was hoped, therefore, that the identification of amino and imino bending frequencies would be easier in the sulphonamides than in the carboxyamides.

Unfortunately the well-known absorption due to the benzene ring at about 1500 and 1600 cm.$^{-1}$ clouds the issue in some of the compounds, but methanesulphonamide shows a band at 1583 cm.$^{-1}$ which can be attributed to the amino deformation vibration, and the other unsubstituted sulphonamides have bands in this neighbourhood also. *N*-Methylmethanesulphonamide shows a moderately weak band at 1626 cm.$^{-1}$ which may be due to the imino deformation, but the *N*-monosubstituted sulphonamides in general do not seem to show any band characteristic of this vibration : certainly there is no band near 1560 cm.$^{-1}$, which is the frequency near which the imino deformation probably occurs in *N*-monosubstituted amides (Richards and Thompson, *loc. cit.*).



Characteristic Frequencies of the N–H *Stretching Vibrations.*—In the unsubstituted carboxyamides in dilute solution in carbon tetrachloride the two N–H stretching vibrations occur at very much the same frequencies as in the primary amines (3400 and 3520 cm.$^{-1}$, according to Richards and Thompson, *loc. cit.*), and in concentrated solution association leads to additional bands at about 100—200 cm.$^{-1}$ below these frequencies. In the solid state only the latter bonds are found.

The unsubstituted sulphonamides are only sparingly soluble in carbon tetrachloride, and show their N–H frequencies at about 3360 and 3455 cm.$^{-1}$, these values falling to 3265—3285 and 3340—3365 cm.$^{-1}$ in the solid. No sign of association can be detected at the concentrations attainable in carbon tetrachloride solution, though the very weak band at 3270 cm.$^{-1}$ in the solution of benzenesulphonamide may be due to such association. Sulphanilamide is completely insoluble in carbon tetrachloride and can only be studied in the solid, where it shows bands at 3395 and 3450 cm.$^{-1}$, attributable to the " amino " $-NH_2$ group, and at 3250 and 3330 cm.$^{-1}$, attributable to the N–H vibrations of the sulphonamide group. The latter are slightly lower in frequency than the corresponding bands for the other unsubstituted sulphonamides studied, which is understandable if the form (I) contributes appreciably to the structure of the molecule, as is indicated by Kumler and Halverstadt's dipole-moment measurements (*loc. cit.*). The greater negative charge on the oxygen atoms will attract more strongly the hydrogen atoms of the sulphonamido-group of the adjacent molecule. The frequencies of the " amino " NH_2 group are not far below those for a " free " NH_2 group, which suggests that this NH_2 group is relatively free, even in the solid state. The high frequencies are also in accord with the presence of structure (I), involving the $=NH_2^+$ group, where it may be expected that the N–H frequencies will be raised by the presence of the positive charge on the nitrogen atom (Flett, *Trans. Faraday Soc.*, 1948, **44**, 767).

The *N*-monosubstituted sulphonamides show their N–H vibration at about 3390 cm.$^{-1}$ in dilute solution in carbon tetrachloride. This value is about 40 cm.$^{-1}$ lower than that for the corresponding amides, and this is undoubtedly due to the strongly electronegative sulphonyl group, which will tend to weaken the N–H bond. Parallel to this effect is the great increase in acidity in passing from an amide to a sulphonamide, which can be as acid as a phenol (Bell and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2905). In addition to the

3390 cm.$^{-1}$ band, the carbon tetrachloride solutions also show a band at about 3270 cm.$^{-1}$, which on dilution becomes weaker relative to the 3390 cm.$^{-1}$ band, and this behaviour, reminiscent of that of the *N*-monosubstituted amides, suggests that the 3270 cm.$^{-1}$ band is due to associated molecules, whereas the 3390 cm.$^{-1}$ band is due to monomeric molecules. Some of the compounds (see Table 2) have a slight shoulder on the side of the 3390 cm.$^{-1}$

TABLE 2.

Ref. No.	S–O Stretching vibrations (cm.$^{-1}$) CCl_4 Solution		S–O Stretching vibrations (cm.$^{-1}$) Solid		O–H and N–H Stretching vibrations (cm.$^{-1}$) CCl_4 Solution						O–H and N–H Stretching vibrations (cm.$^{-1}$) Solid		
					Unsubstituted sulphonamides								
18	1162	1362	1169	1336	—	3455	3360	—	—	—	3340	3265	3130
8	1159[1]	—	1160	1336[2]	—	3455	3355	—	—	—	3360	3265	—
9	1161	1363	1155	1330[2]	—	3455	3355	3270[1]	—	—	3365	3285	—
11	Insoluble		1152	1337	Insoluble				3450	3390	3330	3250	—
					N-Monosubstituted sulphonamides								
19	1159	1333	1135 1155	1315	—	3406[6]	3300[6]	—	—	—	—	3300	—
17	1160	1348	1154	1327	—	3390[5]	3265[6]	—	—	—	3260	3225[4]	—
10	1166	1333 1348[2]	1160	1333	3390[4,5]	3380[5]	3260[6]	—	—	—	—	3215	—
13	1170	1342	1161	1334	—	3385[5]	3265[6]	—	—	—	—	3270	—
14	1170	1347	1165	1348	—	3390[5]	3245[6]	—	—	—	—	3335	—
20	1166	1336	1161	1322	3400[5]	3385[4,5]	3280[6]	—	—	—	—	3265	—
7	1165	1339	1164	1345	—	3380[5]	3250[6]	—	—	—	—	3275	—
12	1162	1354	1164	1377	—	3400[1]	—	—	—	—	3405	3100	—
					NN-Disubstituted sulphonamides								
16	1161	1343 1358	1161	1337	—	—	—	—	—	—	—	—	—
4	1159[1] 1178	1363 1370	1155	1350	—	—	—	—	—	—	—	—	—
6	1172	1363	1158	1346	—	—	—	—	—	—	—	—	—
21	1169	1366	1159	1348	3635	3550	—	—	—	3475[4]	3390[3]	—	—
15	1160	1366	1171	1336	—	3440	—	—	—	—	3335	3295	—
					Molecular compound								
2	1168	1341 1361	1158	1340	3635	3550	—	—	—	3455	3280[1]	3155[1]	—
	—	—	—	—	—	3380[5]	3250[6]	—	—	—	—	—	—
					Reference compounds								
22	—	—	—	—	3640	3440[4]	3410	—	—	—	—	3395[3]	—
1	—	—	—	—	3640	3440[4]	3410	—	—	—	3420[1,4]	3365[3]	—
23	—	—	—	—	3640	3485[3]	—	—	—	—	—	3370[3]	—
5	—	—	—	—	—	—	3410	—	—	—	3392	3340[4]	—
3	—	—	—	—	—	—	3435	—	—	—	3400	—	—
24	—	—	—	—	—	—	3440	3365[3]	—	—	—	3260[3]	—
25	—	—	—	—	—	—	3435	—	—	—	3380	—	—

[1] Very weak. [2] Absorption maximum. [3] Broad. [4] Shoulder. [5] Relative intensity increases with dilution. [6] Relative intensity decreases with dilution.

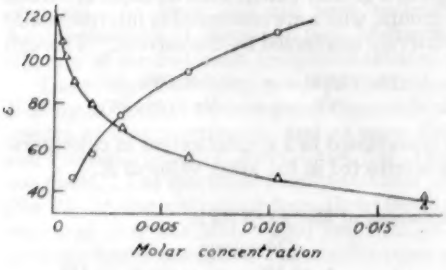
band. The reason for this is obscure, but is possibly to be sought in the existence of two equilibrium positions of the hydrogen atom attached to the nitrogen [cf. an analogous effect observed in the O–H vibration band of benzyl alcohol (Fox and Martin, *Trans. Faraday Soc.*, 1940, **36**, 897)]. The intensity of the shoulder relative to the main peak remains unchanged on dilution, which seems to preclude the shoulder's being due to some form of associated molecule. An interesting difference between the sulphonamides and the amides is that the "associated" band in the former is quite sharp, whereas in the latter it is broad and ill-defined. There is strong evidence that the association of *N*-monosubstituted amides takes place through the formation of chain polymers (Badger and Rubalcava, *Science*, 1953, **117**, 465; Worsham and Hobbs, *J. Amer. Chem. Soc.*, 1954, **76**, 206), whereas the evidence available on the association of *N*-monosubstituted sulphonamides (Le Fèvre and Vine, *loc. cit.*) points to the formation of cyclic molecules on association. The "associ-

ated " band in the *N*-monosubstituted sulphonamides persists even at concentrations below 0·001M in carbon tetrachloride solution, whereas in acetanilide, for instance, it is of negligible intensity below 0·003M, and in the secondary amines there is no appreciable association at concentrations as high as 0·1M. In the solid state the *N*-monosubstituted sulphonamides show a sharp band at almost the same position as the " associated " band found in solution, so that it may be assumed that the same type of association occurs both in the solid and in solution.

To study further the nature of the association, quantitative measurements were made on solutions of methanesulphonanilide in carbon tetrachloride and in chloroform. In chloroform solution the " free " and " associated " bands occur at 3375 and 3270 cm.$^{-1}$. The half-width in carbon tetrachloride solution of the " free " N–H band is 36 cm.$^{-1}$ and that of the " associated " band 66 cm.$^{-1}$, the corresponding figures for chloroform solution being 38 and about 80 cm.$^{-1}$, respectively. These half-widths do not vary appreciably with concentration, nor do the shapes of the bands, so that for comparative purposes the extinction coefficients measured at the peaks of the bands can be used instead of the integrated intensities.

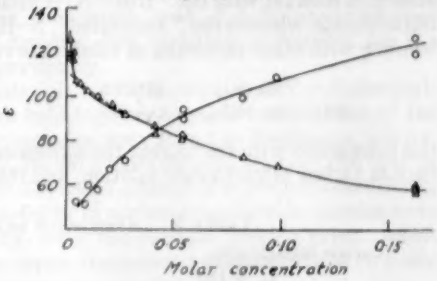
Figs. 1 and 2 show the values, in carbon tetrachloride and chloroform solution respectively, of $\varepsilon = D/cl$ for the " free " and " associated " bands, where D is the optical density

FIG. 1. *Absorption of* $Me{\cdot}SO_2{\cdot}NHPh$ *in* CCl_4 *solution.*



△ 3390 cm.$^{-1}$ band.
○ 3265 cm.$^{-1}$ band.

FIG. 2. *Absorption of* $Me{\cdot}SO_2{\cdot}NHPh$ *in* $CHCl_3$ *solution.*



△ 3375 cm.$^{-1}$ band.
○ 3270 cm.$^{-1}$ band.

at the peak of the band, c is the stoicheiometric concentration of $Me{\cdot}SO_2{\cdot}NHPh$ in formula-weights per litre, and l the path length in cm. As infinite dilution is approached it may be assumed that only the monomer is present, so that the limiting value as $c \to 0$ of D/cl for the " free " band will be ε_m, the molar absorbance of the monomer. If c_m and c_a are the stoicheiometric concentrations of the monomer and the associated molecules respectively, then $c = c_m + c_a$. Let γ be the degree of association, defined by $\gamma = c_a/c$, then $\gamma = 1 - c_m/c = 1 - \varepsilon/\varepsilon_m$, and can be calculated for any concentration from measurements on the " free " band alone. If all the non-monomeric molecules contribute equally to the density of the " associated " band and do not contribute to the " free " band, the plot of ε for the associated band against γ should be a straight line.

It will be seen from the curve for the chloroform solution that there is some ambiguity about the extrapolation to infinite dilution, an ambiguity which is not removed by plotting the results on a logarithmic scale. The rapid rise of ε at concentrations below 0·004M was verified by two completely independent series of measurements, though on account of inaccuracies inherent in the measurement of the absorption of very dilute solutions the experimental points show a fair scatter.

When γ is plotted against ε for the " associated " band, both for carbon tetrachloride and chloroform solutions, a straight line is obtained, at any rate down to concentrations where the exact measurement of ε for the " associated " band becomes impossible. There are thus good grounds for the assumption that only one type of associated molecule exists to any appreciable extent in the solutions under consideration. If it is assumed to be the

ring dimer (IV), the law of mass action gives $K = \gamma/2c(1-\gamma)^2$. Table 3 shows the values of γ and of K calculated on this basis. The ε values for carbon tetrachloride solution readily yield on extrapolation a value $\varepsilon_m = 120$, and the two sets of figures given for chloroform solutions show the values calculated by extrapolation with and without the inclusion of the points below 0·004M.

It is clear that K remains constant to within the limits of experimental error in carbon tetrachloride solution, and, if the points below 0·004M are neglected, in chloroform solution also. There is certainly no drift of the K values over the concentration ranges studied. The relatively large random variation in K values is due to the high sensitivity of the function $\gamma/(1-\gamma)^2$ to small changes in γ, and since γ is dependent on an extrapolated quantity ε_m, and the ε values in the region where the extrapolation has to be made are inherently somewhat inaccurate, the constancy of K is very satisfactory.

Association takes place to a much greater extent in carbon tetrachloride than in chloroform solution, a result which is entirely in agreement with Fox and Martin's observations (*Proc. Roy. Soc.*, **1937**, **162**, *A*, 419) on the association of aromatic alcohols. If the higher absorption values for very dilute chloroform solutions are accepted as being real, the data can be interpreted to point to the existence in very dilute solution of appreciable amounts of the " chain " dimer (V). The " free " vibration occurs at a frequency about 15 cm.$^{-1}$ lower in chloroform than in carbon tetrachloride solution, while the " associated " N–H vibration occurs at almost the same frequency in both solvents. Clearly, the chloroform molecules interact with the " free " N–H groups to a greater extent than do those of carbon tetrachloride, whereas the " associated " N–H groups, which are concerned in intermolecular bonding with other molecules of solute, are relatively unaffected by the solvent. Through

(IV) Me–SO_2 . . . HN–Ph / Ph–NH . . . O_2S–Me

Me·SO_2NH – – – O_2S·NH·Ph (V)
Ph Me

this interaction with the solvent the monomer is stabilised to a greater extent in chloroform than in carbon tetrachloride solution, and this is reflected in the lower value of K.

TABLE 3. *Association in solutions of* Me·SO_2·NHPh.

Carbon tetrachloride			Chloroform				
	$\varepsilon_m = 120$			$\varepsilon_m = 130$		$\varepsilon_m = 112$	
c, M	γ	K	c, M	γ	K	γ	K
0·0160	0·693	223	0·160	0·540	7·98	0·468	5·17
0·0130	0·656	213	0·120	0·498	8·23	0·421	5·23
0·0100	0·613	205	0·080	0·434	8·47	0·340	4·88
0·0070	0·558	204	0·040	0·333	9·36	0·228	4·78
0·0050	0·513	217	0·020	0·260	11·9	0·145	4·96
0·0030	0·422	211	0·015	0·238	13·7	0·120	5·17
0·0020	0·363	224	0·010	0·217	17·7	0·093	5·65
0·0010	0·263	242	0·005	0·185	27·9	0·054	5·76
0·0005	0·158	223	0·0025	0·135	36·1	0·033	5·53
			0·0015	0·104	43·2	0·022	(7·67)
	Mean	218				Mean	5·24

Experiments on the molecular compound (No. 2) and on *N*-ethyltoluene-*p*-sulphonamide in carbon tetrachloride solution over the concentration range 0·001—0·014M showed similar results, with the values of K of about 133 and 121 respectively.

Le Fèvre and Vine (*loc. cit.*) measured the orientation polarisation of the closely similar compound *p*-Me·C_6H_4·SO_2·NHMe at different concentrations in benzene, chloroform, and ether solutions, and on the assumption that the associated form of the molecule has zero dipole moment, calculated values of γ and K in benzene solution for association to a cyclic dimer. From their figures for chloroform solutions the corresponding values have been calculated for this solvent also (Table 4). For ease of comparison with the present work, molar concentrations, c, as well as weight fractions, w_1, are given. Le Fèvre and Vine found an appreciable drift of the K values in benzene solution, but in chloroform, though the K values are somewhat erratic, there is no apparent drift. It seems then that over the

range of concentrations studied by Le Fèvre and Vine association takes place to dimers only, and that the dipole moment of the dimeric molecule is zero in chloroform solution. This being so, it is difficult to see why the moment should be non-zero in benzene solution, and the drift of K in this solvent must then be attributed to failure of the mass-action law brought about by the presence of more than one type of associated molecule.

TABLE 4. *Calculation of results from Le Fèvre and Vine's data on* p-$Me{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHMe$ *in chloroform solution.*

10^5w_1	245	353	543	868	1282	1977	3402	6326
c	0·0196	0·0282	0·0434	0·0693	0·1023	0·1575	0·2704	0·5002
γ	0·056	0·067	0·117	0·143	0·180	0·232	0·307	0·429
K	1·60	1·36	1·74	1·41	1·31	1·25	1·18	1·32

It may be noted that infra-red spectroscopy provides a more rigorous means of investigating this type of association than do dielectric measurements, since in the latter method the dubious assumption has to be made that the dimer has zero dipole moment.

Structure of the Molecular Compound.—Treatment of *N*-*p*-diphenylyltoluene-*p*-sulphonamide with 2-bromoethanol (Baxter, Cymerman-Craig, and Gilbert, *loc. cit.*) gave a 1 : 1 molecular compound of the starting sulphonamide and the desired *N*-*p*-diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide, which could itself not be obtained from the molecular compound. Two substances of similar structure but lacking the hydroxyl group, *N*-*p*-diphenylyl-*N*-ethyl- and *N*-*p*-diphenylyl-*N*-2′-methoxyethyl-toluene-*p*-sulphonamide, were prepared. As these did not form molecular compounds with *N*-*p*-diphenylyltoluene-*p*-sulphonamide, it appeared that hydrogen bonding was probably responsible for the stability of the molecular compound isolated previously.

The study of the way in which the molecules of *N*-*p*-diphenylyl- and *N*-*p*-diphenylyl-*N*-2′-hydroxyethyl-toluene-*p*-sulphonamide are held together requires examination of the spectra of 2-aminoethanols, and as some discrepancies were found in Bergmann, Gil-Av, and Pinchas's paper (*J. Amer. Chem. Soc.*, 1953, **75**, 68) a more detailed study of two spectra was made. The spectra of 2-anilinoethanol (No. 22) and *N*-phenyl-*N*-*n*-propylaminoethanol (No. 23) at concentrations from about 0·002 to 0·15M in carbon tetrachloride solution were measured over the 3000—4000 cm.$^{-1}$ range by using the calcium fluoride prism, which gives far better resolution and enables more accurate frequency measurements to be made than did the sodium chloride prism used by the previous workers.

Bergmann *et al.* found that 2-anilinoethanol in carbon tetrachloride solution shows bands at 3590 cm.$^{-1}$ (due to " free " O–H vibrations) and 3360 cm.$^{-1}$ (attributed to intramolecularly bonded O–H · · · N vibrations). The occurrence of the expected N–H vibration was not mentioned, though Bergmann, in a private communication, says : " We have based our conclusions on the observation that the observed effect [the occurrence of a band in the 3350—3450 cm.$^{-1}$ region] occurs in the same way for tertiary and secondary amines. As in the former no NH vibration is possible, we have assumed that the effect is actually due to the intramolecular hydrogen bond."

Repetition of Bergmann's work showed that for both 2-anilino- and 2-*N*-*p*-diphenylylamino-ethanol (Nos. 22 and 1) the " free " O–H vibration band occurred at 3640 cm.$^{-1}$, and the other band occurred at 3410 cm.$^{-1}$ with a shoulder at 3440 cm.$^{-1}$. Both bands were sharp. *N*-*p*-Diphenylyl-2-methoxyethylamine (No. 5) shows its N–H vibration at 3410 cm.$^{-1}$, so it seems that the 3410 cm.$^{-1}$ band of 2-anilinoethanol is the N–H vibration, and the shoulder at 3440 cm.$^{-1}$, which Bergmann's instrument failed to resolve, can then be attributed to the intramolecular O–H · · · N vibration. The intensity ratios of the 3410, 3440, and 3640 cm.$^{-1}$ bands are independent of concentration, which rules out the possibility that any of these bands might be due to intermolecular bonding. Remeasurement for *N*-phenyl-*N*-*n*-propylaminoethanol (No. 23) for which Bergmann claimed bands at 3600 and 3380 cm.$^{-1}$, showed a sharp band at 3640 cm.$^{-1}$ (clearly due to the " free " O–H vibration) and a very broad band, centred at about 3485 cm.$^{-1}$, apparently due to O–H · · · N vibrations. Bergmann states that in all cases the " free " O–H band is weak in comparison with the O–H · · · N band, but the present measurements show that this is not so : both in the secondary and the tertiary aminoethanols studied the intensity of the " free " O–H band

was at least as great as that of the O–H · · · N band. In the tertiary compound the broad O–H · · · N band resembles in shape and frequency the bands due to intermolecular association in alcohols, and since its intensity, relative to that of the " free " O–H band, seems to decrease with decrease of concentration it is probably due in part to intermolecular O–H · · · O bonds.

The molecular compound (No. 2) and *N*-*p*-diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide (No. 21) were studied to the limit of concentration imposed by solubility in carbon tetrachloride (*ca.* 0·02M), and each shows two sharp absorption peaks, with intensities of the same order of magnitude, at 3635 and 3550 cm.$^{-1}$. The higher-frequency band can readily be ascribed to " free " O–H vibrations, but the lower one is not considered to be due to dimerisation through O–H · · · O–H linkages, as the frequency of such a band would be about 3500 cm.$^{-1}$ (Smith and Creitz, *J. Res. Nat. Bur. Stand.*, 1951, **46**, 145); moreover, at concentrations below 0·02M the concentration of dimers would be extremely small. In view of the above discussion it is extremely unlikely that the 3550 cm.$^{-1}$ band is due to intramolecular O–H · · · N bonding,* so it must be attributed to O–H · · · O_2S bonds, which could be formed intra- or inter-molecularly. Now in both compounds Nos. 2 and 21 the ratio of the intensity of the 3550 cm.$^{-1}$ band to that of the 3635 cm.$^{-1}$ band decreases with dilution, a fact which suggests that the bonds are intermolecular. At any given molar concentration this intensity ratio is greater for the molecular compound No. 2 than for compound No. 21, which also points to the existence of intermolecular bonds, for the concentration of molecules with SO_2 groups, suitable as acceptors for the proton of the OH group, is twice as great in the former as in the latter.

The relatively small shift of the O–H frequency from the free state to the O–H · · · O_2S state (85 cm.$^{-1}$) is in accordance with the known weakness of the SO_2 group as a chelating agent. For instance, Amstutz, Chessick, and Hunsberger (*Science*, 1950, **111**, 305; *J. Amer. Chem. Soc.*, 1951, **73**, 1220) found that, even in a compound such as *o*-hydroxydiphenyl sulphone, where conditions are ideal for chelation, the shift of the O–H frequency is only 300 cm.$^{-1}$, as compared with a shift of at least 600 cm.$^{-1}$ found for *o*-hydroxydiphenyl sulphoxide or for *o*-hydroxyacetophenone (Martin, *Nature*, 1950, **166**, 474).

The existence of intermolecular O–H · · · O_2S bonding was substantiated by the following experiments: (*a*) Addition of *N*-*p*-diphenylyl-*N*-ethyltoluene-*p*-sulphonamide (No. 4) to a solution of 2-*N*-*p*-diphenylylaminoethanol (No. 1) in carbon tetrachloride solution leads to the development of an extra O–H band at 3570 cm.$^{-1}$, whose intensity relative to the original O–H band at 3640 cm.$^{-1}$ increases with increasing concentration of compound No. 4. It could, of course, be argued that the new band is due to an intermolecular O–H · · · N bond between the O–H group of compound No. 1 and the tertiary nitrogen atom in compound No. 4, but this is ruled out by the fact that no such band appears when a solution of compound No. 1 is mixed with tribenzylamine, a compound in which the nitrogen, being much more basic than in compound No. 4, would be more likely to attract the proton from the OH group. The N–H vibration band in compound No. 1, at 3410 cm.$^{-1}$, is completely unaffected by mixing either with compound No. 4 or with tribenzylamine. (*b*) The addition of compound No. 4 to compound No. 21 in solution increases the intensity of the 3550 cm.$^{-1}$ band and decreases that of the 3635 cm.$^{-1}$ band.

In these experiments, on account of the difficulties of measuring small changes in band intensity in a region where water vapour absorbs fairly strongly, it is necessary to use a concentration of compound No. 4 somewhat greater than that of compound No. 1 or 21. Because of the very low solubility of compound No. 7 it is not possible to demonstrate with certainty interaction in solution between this compound and compound No. 21, but the above experiments leave no doubt that such interaction does occur through the O–H · · · O_2S linkage.

Evidence shows clearly that, in the solid state, the OH group takes part in the bonding between the two components of the molecular compound. Both compounds Nos. 1 and 21 show typical spectra of hydroxy-compounds, having broad bands centred at 3365 and

* It is noteworthy that there is no trace in No. 21 of OH · · · N bonding of the type found in *N*-*n*-propyl-2-anilinoethanol (No. 23). This is readily explained by the much lower basicity of the nitrogen atom in the former compound and its consequent inability to accept the proton from the OH group.

3390 cm.$^{-1}$, respectively, with half-widths of ~240 and ~170 cm.$^{-1}$, indicating the existence of chains of polymers (Smith and Creitz, *loc. cit.*), whereas in compound No. 2 there is an intense and fairly sharp band at 3455 cm.$^{-1}$ (half-width ~90 cm.$^{-1}$). The shoulder occurring at 3475 cm.$^{-1}$ in No. 21 is taken to indicate that intermolecular O–H · · · O_2S bonds exist to some extent in this compound also. The N–H frequency in compound No. 2 occurs at almost exactly the same frequency, 3280 cm.$^{-1}$, as in compound No. 7, which supports the view that this group plays no part in holding together the two components of the molecular compound.

It is concluded then that compounds Nos. 7 and 21 are held together in the molecular compound (No. 2) through the linkage O–H · · · O_2S, and it is also shown that interaction between these two compounds takes place in solution through the same linkage and by no other form of hydrogen bond.

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Steroids and Walden Inversion. Part XX. A Kinetic Study of the Acetolysis of Cholesteryl Bromide.*

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Acetolysis of cholesteryl bromide in the presence of added acetate has been shown to proceed by a unimolecular heterolysis, thereby confirming the view (Shoppee, *J.*, 1946, 1147) that replacement, accomplished with retention of configuration, involves the 3β-cholesteryl cation. In the absence of added acetate, the reaction is catalysed by hydrogen ions and is reversible, but it appears that the rate-determining stage is the catalysed ionisation of the bromide. In the presence of acetic anhydride, the reaction gives a first-order rate constant which is insensitive to the concentration of anhydride over a wide range. An explanation of this result is offered. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the reaction are compared with the corresponding values for the acetolysis of cholesteryl toluene-*p*-sulphonate; it is concluded with Simonetta and Winstein (*J. Amer. Chem. Soc.*, 1954, 76, 18) that stabilisation of the carbonium ion resulting from the heterolysis by the π-electrons of the 5 : 6-double bond is of the order of a few kcal. mole^{-1} only.

EARLIER (Shoppee, *J.*, 1946, 1147) it was shown that acetolysis of cholesteryl chloride occurred with complete retention of configuration at $C_{(3)}$. This behaviour, which was shown by configurational studies to be typical of replacement reactions with weakly nucleophilic reagents at $C_{(3)}$ in Δ^5-steroids, is in marked contrast to the corresponding reactions at $C_{(3)}$ in saturated steroids, which proceed with inversion of configuration (*idem, ibid.*, p. 1138). It was suggested that for nucleophilic substitution reactions at $C_{(3)}$ in Δ^5-steroids the π-electrons of the 5 : 6-double bond not only facilitate ionisation of the atom or group attached to $C_{(3)}$ leading to a unimolecular heterolysis, but also preserve configuration at $C_{(3)}$ (sp^3-hybridisation with a vacant orbital) in the resulting carbonium ion, by interaction (partly electrovalent, partly covalent) with the positive charge. This proposed mechanism has been examined in greater detail more recently by Shoppee and Summers (*J.*, 1952, 3361) in relation to the 3 : 5-*cyclo*steroid rearrangement, whilst Simonetta and Winstein (*J. Amer. Chem. Soc.*, 1954, 76, 18) have applied a molecular-orbital treatment to estimate the stabilisation due to the π-electron delocalisation.

* Part XIX, *J.*, 1954, 4224, in line 13 of which "kinetic" and "thermodynamic" should be interchanged.

Winstein and Adams (*ibid.*, 1948, **70**, 838) reported that acetolysis of cholesteryl toluene-*p*-sulphonate in anhydrous acetic acid either alone or in the presence of added acetate, gave first-order rate constants; Wallis, Hafez, and Halsey (*Science*, 1949, **110**, 474) also found a first-order rate constant for the hydrolysis of cholesteryl toluene-*p*-sulphonate in aqueous acetone in the presence of acetate ion and showed that the rate of hydrolysis increased with increasing ease of separation of the 3β-substituent as the anion: p-$C_6H_4Me{\cdot}SO_3^- < Ph{\cdot}SO_3^- <$ p-$NO_2{\cdot}C_6H_4{\cdot}SO_3^-$, thereby providing experimental confirmation of a mechanism of S_N1 type. It was of interest to ascertain whether the cholesteryl halides would behave similarly on acetolysis and to obtain additional data which might contribute to a more detailed analysis of the reaction mechanism.

Preliminary observations showed that acetolysis of the more readily available cholesteryl chloride was inconveniently slow for a detailed kinetic study. Thus even at 95° the reaction in the absence of added acetate was only about one-third complete after 72 hours. Moreover difficulty was experienced in following the course of the reaction by titrating the liberated hydrogen chloride. Contrary to the work of Steigman and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 2536) it was found that the titration of approximately 0·02M-solutions of hydrogen chloride in acetic acid against sodium acetate as a base could not be effected with any degree of accuracy when crystal-violet was used as indicator. Further, no sharp end-point could be observed on back-titration although a number of other indicators covering a wide range of pH values was tried. This difficulty may be attributed to the low strength of hydrogen chloride in acetic acid solution. Smith and Elliot (*ibid.*, 1953, **75**, 3566) have calculated the dissociation constants of certain acids in acetic acid solution from the conductance results obtained by Kolthoff and Willman (*ibid.*, 1934, **56**, 1007). The dissociation constants of perchloric, hydrobromic, sulphuric, and hydrochloric acid were computed to be 9×10^{-7}, $1{\cdot}9 \times 10^{-7}$, $7{\cdot}4 \times 10^{-9}$, and $5{\cdot}1 \times 10^{-10}$ respectively. These values give the approximate relative strengths of the four acids as $HClO_4 : HBr : H_2SO_4 : HCl =$ 42 : 19 : 4 : 1. Shkodin and Izmailov (*J. Gen. Chem., U.S.S.R.*, 1950, **20**, 39) have reported slightly higher values for the dissociation constants of these acids but the relative strengths are the same as those already quoted. It is evident that hydrogen chloride is a very weak acid in acetic acid solution and that chloride solutions are extensively solvolysed.

Acetolysis of cholesteryl bromide was found to be more convenient for study since at 95° the reaction was about half complete after seven hours and, as a consequence of the

TABLE 1. *Acetolysis of approx.* 0·02M-*solutions of cholesteryl bromide in the presence of* 0·05M-*diphenylguanidinium acetate, at* 94·8° ± 0·15°.

Time (min.)	10^2M	Reaction (%)	10^2k_1 (min.$^{-1}$)	Time (min.)	10^2M	Reaction (%)	10^2k_1 (min.$^{-1}$)
90	2·018	13·7	1·63	420	2·089	41·4	1·27
120	2·106	16·5	1·50	705	2·039	56·9	1·20
150	2·144	21·7	1·63	900	2·037	62·6	1·09
200	2·008	25·5	1·47	1080	2·132	66·2	1·02
240	1·888	29·0	1·43	1200	2·108	70·3	1·01
247	2·082	28·4	1·35	1440	2·133	73·7	0·93
300	2·045	33·5	1·36	1669	2·135	76·9	0·88
360	2·156	40·2	1·43	1800	2·126	78·3	0·85

TABLE 2. *Acetolysis of approx.* 0·02M-*solutions of cholesteryl bromide in the presence of* 0·02M-*diphenylguanidinium acetate, at* 94·8° ± 0·15°.

Time (min.)	10^2M	Reaction (%)	10^2k_1 (min.$^{-1}$)	Time (min.)	10^2M	Reaction (%)	10^2k_1 (min.$^{-1}$)
90	2·100	9·6	1·12	300	2·156	23·1	0·88
129	2·129	13·0	1·08	900	2·047	44·0	0·65
180	2·048	16·0	1·21	1440	2·079	55·3	0·56

greater strength of hydrogen bromide in acetic acid, no difficulty was experienced in following the reaction by titration of the liberated acid. A selection of results obtained for the acetolysis of approximately 0·02M-cholesteryl bromide in 0·05M- and 0·02M-diphenylguanidinium acetate solution in anhydrous acetic acid at 94·8° ± 0·15° is presented in Tables 1 and 2. For small intervals, the experimental limitation of ±0·01 ml. in titration of the liberated hydrogen bromide introduces an uncertainty of about ±5% in the individual

values of k, but this becomes progressively less as the duration of the reaction increases. From Tables 1 and 2, it will be seen that within the limits of experimental error the reaction, in its early stages, does not deviate significantly from the usual first-order kinetic relation $dx/dt = k_1x(a - x)$ but, as the reaction proceeds, the value of the specific rate constant becomes progressively less. From these results, the initial specific rate constants (obtained by extrapolation to zero reaction) in the presence of 0·05M- and 0·02M-diphenylguanidinium acetate are $1·75 \times 10^{-3}$ and $1·25 \times 10^{-3}$ min.$^{-1}$ respectively. When the acetolysis was effected in the presence of sodium acetate instead of diphenylguanidinium acetate, the initial first-order specific rate constants for 0·05M- and 0·02M-solutions of sodium acetate were $0·70 \times 10^{-3}$ and $0·61 \times 10^{-3}$ min.$^{-1}$ respectively. Thus, the rate is different in the presence of the same concentration of different acetates (cf. Steigman and Hammett, *loc. cit.*). As will be seen later, the reaction in the pure solvent is complicated by autocatalysis, but the initial specific rate constant is $0·25 \times 10^{-3}$ min.$^{-1}$; increasing the concentration of added acetate ions thus accelerates the reaction and, when the influences of diphenylguanidinium and sodium acetates are compared, the effect is seen to depend on the nature of the added electrolyte. We are of the opinion that these results are explicable on the basis that the acetolysis involves the following unimolecular heterolysis :

$$RBr \underset{(2)}{\overset{(1)}{\rightleftharpoons}} R^+ + Br' \xrightarrow[(3)]{Ac'} RAc + Br'$$

Hughes, Ingold, *et al.* (*J.*, 1940, 960 *et seq.*; 1952, 2488) have shown that the reversible nature of the rate-determining ionisation step (1) leads to a progressive retardation of the reaction irrespective of whether the overall reaction is reversible or otherwise. As the reaction proceeds, the concentration of bromide ion resulting from stage (3) increases, thereby causing stage (2) to become more significant and to diminish the rate. In such circumstances, it is necessary to employ the modified kinetic expression $dx/dt = k(a - x)/(1 + \alpha x)$, where α is a factor which determines the ability of bromide ion to compete with acetate ion for the carbonium ion R^+ and the factor $(1 + \alpha x)$ determines the extent of departure from the specific rate $(dx/dt)/(a - x)$. Taking α to be approximately 50 is adequate to compensate for the downward drift in the values of k_1 given in Table 1.

We attribute the effect of added acetate ion on the rate of the reaction to the variation in the ionic strength of the solvent. The low dielectric constant of acetic acid (6 at 25° and less at 95°) favours extensive ionic association in this solvent (Fuoss and Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 1019). Since the extent of ion association increases markedly with decreasing ionic diameter, this would account for the difference in rate observed in the presence of diphenylguanidinium acetate and sodium acetate. The latter electrolyte is less dissociated and consequently gives rise to a smaller ionic-strength effect. Similar specific-salt effects have been observed by Steigman and Hammett (*loc. cit.*) for the acetolysis of 1-phenylethyl halides. In an attempt to compensate for the lower ionic strengths of the solutions in Table 2, some of the measurements were repeated in the additional presence of 0·03M-diphenylguanidinium perchlorate. The specific rate constant under these conditions increased to $2·52 \times 10^{-3}$ min.$^{-1}$, so that the ionic-strength effect resulting from the addition of 0·03M-diphenylguanidinium perchlorate is greater than that from 0·03M-diphenylguanidinium acetate. This specific-salt effect is again a consequence of the disparity between the dissociation constants of the two electrolytes.

The reaction products * in the presence of added acetate were established by chromatographic analysis as consisting of cholesteryl acetate and unchanged cholesteryl bromide in amounts which agreed with the rate observations.

The reaction in acetic acid alone presented some unexpected features. From Table 3 it will be observed that the rate of acetolysis increases with time until the reaction is approximately two-thirds complete and then diminishes until a state of equilibrium is

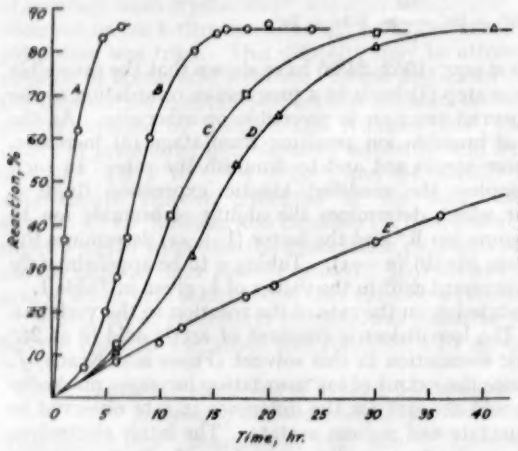
* The acetolysis could lead to the production in reaction (2) of 3 : 5-*cyclo*cholestan-6β-yl bromide when carried out in the presence of added acetate ion or of acetic anhydride, *i.e.*, in the absence of hydrogen bromide, to which as a strong acid 3 : 5-*cyclo*steroids are labile (cf. Shoppee and Summers, *J.*, 1952, 3361, especially 3368); such a process would be kinetically equivalent to the production of cholesteryl bromide in the reassociation process (2), but no such compound could be isolated.

reached corresponding to 85% conversion. These results are represented graphically by curve *B*. Curves *C* and *D* represent the corresponding results obtained for approximately 0·01M- and 0·005M-solutions of bromide respectively. The three curves show that the reaction proceeds to the same equilibrium and their sigmoid form, especially for the more

TABLE 3. *Acetolysis of approx.* 0·02M-*solutions of cholesteryl bromide at* 94·8° ± 0·15°.

Time (min.)	(10^2M)	Reaction (%)	10^3k_1 (min.$^{-1}$)	Time (min.)	(10^2M)	Reaction (%)	10^3k (min.$^{-1}$)
180	1·878	7	0·41	918	2·101	84	2·00
300	1·953	20	0·74	946	2·037	85	2·01
360	1·904	28	0·92	1080	1·900	85	1·76
410	2·085	37	1·13	1200	2·054	86	1·64
540	2·040	60	1·69	1440	2·053	85	1·32
787	2·055	80	2·03	2468	1·989	85	0·76

concentrated solution, indicates that the reaction is autocatalysed. The discrepancy between the initial specific rate constant of $0{\cdot}25 \times 10^{-3}$ min.$^{-1}$ observed under these conditions and the corresponding values obtained in the presence of added acetate is of the order of magnitude expected from an ionic-strength effect. Confirmation of the fact that the hydrogen bromide liberated during the reaction was responsible for the catalysis was



A, *Acetolysis of* 0·02M-*cholesteryl bromide in presence of* 0·017M-*hydrobromic acid.*
B, *Acetolysis of* 0·02M-*cholesteryl bromide.*
C, *Acetolysis of* 0·01M-*cholesteryl bromide.*
D, *Acetolysis of* 0·005M-*cholesteryl bromide.*
E, *Acetolysis of* 0·02M-*cholesteryl bromide in presence of* 0·1M-*acetic anhydride solution.*

obtained from a series of determinations on 0·02M-solutions of cholesteryl bromide which were initially 0·017M with respect to hydrogen bromide. This initial amount of acid resulted in attainment of equilibrium in about 4 hours as compared with 17 hours in its absence (curve *A*). A similar result was obtained with perchloric acid. On the other hand when the reaction was effected in the presence of 0·01M-tetramethylammonium bromide, only a slight increase in rate was detected. It appears therefore that hydrogen ions are responsible for the catalysis and that these are effectively removed by the addition of acetate ions. The increase by a few per cent. observed in the conversion of the bromide resulting from the presence of 0·5M-water is probably due to the increased ionising tendency under these conditions.

Contrary to the above observations on cholesteryl bromide, Winstein and Adams (*loc. cit.*) reported a good first-order rate constant for the acetolysis of cholesteryl toluene-*p*-sulphonate. Moreover, although the reaction was studied until it was about 70% complete, there was no indication that the reaction reached an equilibrium. Re-examination of the kinetics of this reaction at 50° gave a first-order constant of $7{\cdot}5 \times 10^{-3}$ min.$^{-1}$ which agrees with the value of $7{\cdot}9 \times 10^{-3}$ min.$^{-1}$ obtained by Winstein and Adams. The specific rate constant was found to show a slight downward drift with time but, although the reaction was studied until it was 97% complete, there was no evidence either of catalysis or that an equilibrium had been attained.

When the acetolysis of 0·02M-solutions of cholesteryl bromide was carried out in the presence of 0·017M-toluene-*p*-sulphonic acid, no significant change in the rate could be detected. Although toluene-*p*-sulphonic acid is weaker than either perchloric or hydrobromic acid in acetic acid solution (Shkodin and Ismailov, *loc. cit.*), it is difficult to understand the marked difference in behaviour of the bromide and the toluene-*p*-sulphonate. Shoppee and Williams (following paper) have also observed this anomalous behaviour in the acetolysis of *epi*cholesteryl bromide.

A further complication is that, under the conditions employed for acetolysis, the liberated hydrogen bromide can effect decomposition of the steroid molecule, as is shown by the solutions' gradually developing a brown colour.* Chromatographic analyses of the products obtained under these conditions were inconclusive on account of the difficulty experienced in crystallising the oils eluted. The ultra-violet absorption band observed at 213 mμ for ethanolic solutions of these oils probably corresponds to the presence of cholesteryl bromide (Bladon, Henbest, and Wood, *J.*, 1952, 2737), whilst the broad band in the 240-mμ region may be attributed to the presence of cholesta-3 : 5-diene (see Table 25; Dorfman, *Chem. Reviews*, 1953, **53**, 108) formed by elimination. Cholesteryl acetate was found to react with hydrogen bromide in acetic acid solution to give some cholesteryl bromide, thus accounting for the observation made from the kinetic measurements that an equilibrium was established.

Assuming that the reaction, in the absence of added acetate, occurs by the mechanism :

$$RBr \rightleftharpoons R^+ + Br' \overset{AcOH}{\rightleftharpoons} RAc + HBr$$

and that any elimination or other side reaction does not influence the rate, we may write

$$dx/dt = k_1(a - x)x - k_2x^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where a is the initial concentration of cholesteryl bromide, x the extent of reaction at time t, $k_1(a - x)x$ is the rate of the catalysed ionisation of the bromide, and k_2x^2 the rate of the back reaction. Writing x_e for the concentration of hydrogen bromide at equilibrium, we get :

$$k_1(a - x_e)x_e = k_2x_e^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

When equation (2) is used to relate the coefficients k_1 and k_2, the integrated form of equation (1) becomes :

$$ak_1t = \ln \{x/[a(1 - x/x_e)]\} + c$$

The experimentally observed value of x_e is $0{\cdot}85a$. The plot of $\log [x/(a - x/0{\cdot}85)]$ against time was found to be linear. Thus the mechanism envisaged for the reaction appears to be satisfactory and the rate-determining step is the ionisation of the bromide, catalysed by hydrogen ions, the overall reaction being reversible.

During the preliminary investigation of the reaction, the above autocatalysis was found to be absent when a particular specimen of acetic acid was employed as solvent. The difference in behaviour was subsequently traced to the presence of acetic anhydride as an impurity in this solvent. A systematic study of the effect of acetic anhydride on the rate of acetolysis of cholesteryl bromide revealed, as shown in Table 4, that the rate was independent of the concentration of acetic anhydride up to 1M. Even in a solvent containing

TABLE 4. *Acetolysis of cholesteryl bromide in the presence of acetic anhydride.*
Temp. 94° ± 0·15°.

Concn. of bromide (10^3M)	1·892	1·921	1·873	1·823	1·816	2·068	1·978
Concn. of anhydride (M)	0·05	0·10	0·25	0·5	1·0	60%	100%
Time (min.)	1230	1230	1835	1020	1230	1528	1650
Reaction (%)	26·7	25·7	36·7	22·7	27·7	35·8	0
10^3k_1 (min.$^{-1}$)	0·252	0·242	0·250	0·252	0·263	0·290	—

* Work in progress has shown that traces of molecular oxygen in the solution influence the development of colour.

60% of acetic anhydride, the change in rate was not more than expected from such a change in the dielectric constant and other properties of the solvent.

Each run made in a solvent containing acetic anhydride gave an excellent first-order rate constant. Since the initial specific rate constant for acetolysis in the pure solvent ($0{\cdot}25 \times 10^{-3}$ min.$^{-1}$) is the same as the rate constant observed in solvent containing acetic anhydride (see also the Figure), it follows that the latter must effectively remove the hydrogen bromide which is responsible for the catalysis. A plausible explanation for the removal of the catalytic species by acetic anhydride emerges from Mackenzie and Winter's proposal (*Trans. Faraday Soc.*, 1948, **44**, 159) that in acetic acid–acetic anhydride solutions of mineral acids the strongly electrophilic solvated proton, $AcOH_2^+$, reacts with acetic anhydride according to the equation, $AcOH_2^+ + Ac_2O \rightleftharpoons Ac^+ + (AcOH)_2$. The equilibrium would not interfere with the titration procedure since the resulting acetyl bromide is known to behave as a monobasic acid in acetic acid solution and can be titrated against sodium acetate (Usanovitch and Yatsimirsku, *J. Gen. Chem. U.S.S.R.*, 1941, **11**, 954, 959).

Measurements made on the acetolysis of cholesteryl bromide in the presence of 0·1M-acetic anhydride at 84·8° gave a specific rate constant of $9{\cdot}1 \times 10^{-5}$ min.$^{-1}$. Combining this value with the smoothed value of $0{\cdot}25 \times 10^{-3}$ min.$^{-1}$ observed at 94·8° gives 26·5 kcal. mole^{-1} for the energy of activation as calculated according to the Arrhenius equation. It is reasonable to assume that this also represents the energy of activation for the uncatalysed reaction. The heat of activation ($\Delta H^{\ddagger}$) is 25·8 kcal. mole^{-1} and is 1·4 kcal. mole^{-1} greater than that for cholesteryl toluene-*p*-sulphonate; $\Delta H^{\ddagger}$ is possibly in error by 1 kcal. mole^{-1} because it is based on measurements at two temperatures only, but it is evidently greater than the value (24·4) observed for cholesteryl toluene-*p*-sulphonate. The corresponding value for cholestan-3β-yl bromide is not available (see, however, Simonetta and Winstein, *loc. cit.*, p. 20, footnote 23) so that it is not possible at present to ascertain the extent to which the π-electrons of the 5 : 6-double bond have influenced the activation energy. However, from the value of 27·0 kcal. mole^{-1} for *cyclo*hexyl toluene-*p*-sulphonate (Winstein and Adams, *loc. cit.*) it seems permissible to conclude with Simonetta and Winstein that stabilisation of the carbonium ion by the π-electrons is of the order of a few kcal. mole^{-1} only. The entropy of activation ($\Delta S^{\ddagger}$) for cholesteryl bromide is −13·5 kcal. mole^{-1} deg.$^{-1}$, compared with only −1·0 cal. mole^{-1} deg.$^{-1}$ for the toluene-*p*-sulphonate. Since the rate-determining step is one of ionisation, it follows that there should be a parallelism between the entropy of activation and the entropy of solvation of the ions. Evans and Hamann (*Trans. Faraday Soc.*, 1951, **47**, 40) are of the opinion that it is the change in entropies of solvation which largely determines the change in $\Delta S^{\ddagger}$ values. The larger toluene-*p*-sulphonate ion with its more dispersed charge will orientate the solvent molecules to a smaller extent than the bromide ion. This is consistent with the more negative $\Delta S^{\ddagger}$ value observed for the acetolysis of cholesteryl bromide.

Experimental

For general experimental directions, see *J.*, 1954, 4224. $[\alpha]_D$ are in $CHCl_3$, and ultra-violet absorption spectra were determined in EtOH on a Unicam Sp. 500 spectrophotometer with corrected scale.

Anhydrous Acetic Acid.—Preliminary kinetic measurements showed that the rates were uninfluenced by traces of organic impurities present in " AnalaR " acetic acid and the initial procedure involving distillation over chromium trioxide was therefore omitted. The water content of " AnalaR " acetic acid was determined by direct titration with the Karl Fischer reagent; the titration was satisfactory when carried out quickly and gave a result which agreed with the water content calculated from the lowering of the f. p. of the acid on the assumption that water was the only impurity. The water was removed by refluxing the acid for 36—48 hr. with the calculated amount of acetic anhydride in the presence of a little diphenylguanidinium acetate as a catalyst. Fractional distillation of the products yielded a main fraction boiling at 118·0—118·2°. In subsequent operations, precautions were taken to minimise exposure of the solvent to atmospheric moisture.

Cholesteryl Bromide.—This was prepared by the method of Jones *et al.* (*J.*, 1948, 1787). The

thionyl bromide employed was prepared and purified as described in *Inorg. Synth.*, Vol. I, p. 113. Several recrystallisations from acetone gave cholesteryl bromide, m. p. 98°, $[\alpha]_D^{18}$ −21°.

Cholesteryl Toluene-p-sulphonate.—This (m. p. 132°) was prepared as described by Wallis, Fernholz, and Gephart (*J. Amer. Chem. Soc.*, 1937, **59**, 137).

Diphenylguanidine.—Material of reagent grade was recrystallised four times from ethanol; after drying at 120°, it had m. p. 148°.

Acetic Anhydride.—" AnalaR " material was refluxed over marble for 3 hr. and distilled (b. p. 138°).

Titrations in Anhydrous Acetic Acid.—An approximately 0·05M-solution of perchloric acid in acetic acid, employed as a standard acid, was prepared from 70% aqueous acid of known titer, the calculated amount of acetic anhydride being added to remove the water present. The perchloric acid solution was standardised against a solution of potassium hydrogen phthalate in acetic acid. Crystal-violet was found to be a satisfactory indicator. A semimicroburette, reading to 0·01 ml., was employed and titrations were conducted at a uniform room temperature in order to minimise errors in concentration arising from expansion of the solvent.

Solutions of hydrobromic acid in acetic acid were titrated by adding a known volume of standard diphenylguanidinium acetate solution and determining the excess of base by titration against standard perchloric acid. The end point with crystal-violet as indicator was sharp and reproducible to 0·01 ml. The titration was confirmed by a differential potentiometric method (MacInnes and Dole, *J. Amer. Chem. Soc.*, 1929, **51**, 119), using platinum electrodes in a saturated solution of quinhydrone in acetic acid. On account of the high electrical resistance of such solutions, an electronic pH meter was employed for recording the e.m.f.

In the corresponding titration of hydrochloric acid solutions in acetic acid, the end point was indefinite, although a variety of indicators covering a wide range of pH values was tried.

Rate Measurements.—The velocity of acetolysis was determined in a thermostat, electronically regulated at 94·8° ± 0·15°. A technical product, " Ucepal " (an ethylene glycol derivative), proved to be a convenient thermostatic liquid at this temperature. The sealed ampoule procedure was adopted in order to minimise losses of solvent and hydrobromic acid from the solutions. The low solubility of cholesteryl bromide in acetic acid at room temperature did not permit the preparation of a stock solution and it was necessary to introduce into each tube, separately, a weighed amount of bromide and a measured volume of solvent to give the desired molarity. The solutions, which occupied a volume of between 5 and 10 ml., were made up by weight in each tube. About 50 mg. of bromide, weighed to the nearest 0·01 mg., were used for each determination. Preliminary measurements showed that the reaction proceeded at a negligible rate at room temperature.

Dissolution of the bromide occurred within 30 sec. when the ampoules were immersed in the thermostat and thoroughly shaken. The solutions attained the temperature of the thermostat within 2 min. The reaction was stopped by immersing the ampoule in ice-cold water. When the solutions contained free hydrobromic acid, loss of acid was avoided by opening the ampoule under a solution containing a known volume of standard diphenylguanidinium acetate, and the excess of base was then determined by titration against perchloric acid.

Acetolysis in the pure solvent involved a darkening of the solution towards the end of the reaction. The development of colour was less marked when the solvent contained added base. In the presence of added acetic anhydride the solutions developed a pink colour within about 15 hr. but after about 48 hr. the solutions had darkened to such an extent as to make their titration more difficult.

Determination of the Reaction Products.—A 0·02M-solution (50 ml.) of cholesteryl bromide in a 0·05M-solution of diphenylguanidinium acetate in acetic acid was sealed in a small flask and immersed for 12 hr. in the thermostat at 95°. The mixture was poured into water and extracted twice with ether. After washing successively with water, dilute acid, water, sodium carbonate, and finally with water until neutral, evaporation of the ether yielded an oil which solidified. The solid was chromatographed on aluminium oxide in pentane, and pentane eluates were found to yield cholesteryl bromide, m. p. 95—96°, whilst elution with benzene–pentane mixtures gave cholesteryl acetate, m. p. 116°. The yield of cholesteryl acetate (56%) agreed quantitatively with the conversion of bromide observed by the rate measurements.

The determination was repeated in the absence of a base. The product was extracted with ether and hydrolysed with 5% methanolic potassium hydroxide for 1·5 hr., and the resulting solution poured into water. Ether-extraction gave an oil, about 20% of which was insoluble in methanol and presumably non-steroidal. The methanol-soluble portion was chromatographed on aluminium oxide in pentane. Elution with pentane gave an oil, $[\alpha]_D$ +51° (c, 1·8), $\lambda_{max.}$

213 and 245 mμ, showing a positive test for halogen. Benzene–pentane and benzene eluates yielded traces of oil which could not be crystallised.

Action of Hydrogen Bromide on Cholesteryl Acetate.—An ampoule containing 484 mg. of cholesteryl acetate in 50 ml. of a 0·02M-solution of hydrogen bromide in acetic acid, was kept in a thermostat at 90° for 12 hr. The brown solution was poured into water. Ether-extraction gave a brown oil (452 mg.), which failed to crystallise on nucleation with starting material. The oil was chromatographed on aluminium oxide in pentane. The pentane eluates yielded an oil (356 mg.) which gave a positive Beilstein test and a brown colour in the Rosenheim test. The benzene–pentane and benzene eluates yielded 47 mg. and 17 mg. respectively of brown oil.

Action of Methanolic Potassium Hydroxide on Cholesteryl Bromide.—Cholesteryl bromide (179 mg.) in 100 ml. of 5% solution of potassium hydroxide in methanol was refluxed for 1·5 hr. The product was poured into water and worked up in the usual manner. Evaporation of the ethereal extract gave a light brown oil, 183 mg., which crystallised from acetone to give cholesteryl bromide, m. p. and mixed m. p. 92—94°.

Acetolysis of Cholesteryl Bromide in the Presence of Acetic Anhydride.—An ampoule containing 500 mg. of cholesteryl bromide in 50 ml. of a 0·1M-solution of acetic anhydride in acetic acid was kept at 95° for 24 hr. Working up in the usual manner gave a brown oil (467 mg.). Chromatographic analysis on aluminium oxide gave 353 mg. of an oil from the pentane eluates and 35 mg. of an oil from the benzene–pentane eluates. Attempts to identify these products proved unsuccessful.

One of us (S. M.) acknowledges the financial support of the Swansea Education Authority; we thank Mr. J. R. Lewis, B.Sc., for assistance with the chromatographic analyses, and Glaxo Laboratories Ltd. for gifts of cholesterol.

UNIVERSITY COLLEGE OF SWANSEA, UNIVERSITY OF WALES. [*Received, August 10th*, 1954.]

Steroids and Walden Inversion. Part XXI. A Kinetic Study of the Acetolysis of* epi*Cholesteryl Bromide and Toluene*-p-*sulphonate.*

By C. W. SHOPPEE and D. F. WILLIAMS.

[Reprint Order No. 5734.]

A kinetic study of the acetolysis of *epi*cholesteryl toluene-*p*-sulphonate shows that the reaction is of the first order; the increased rate observed in the presence of added acetate ions is of the magnitude to be expected from an ionic-strength effect. An irreversible unimolecular heterolysis constitutes the rate-determining step and by the elimination of a proton from the resulting carbonium ion leads to cholesta-3 : 5-diene. The reaction is not catalysed by hydrogen ions and is unaffected by the presence of acetic anhydride.

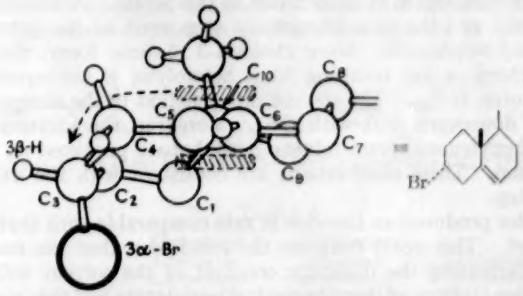
A similar kinetic study of the acetolysis of *epi*cholesteryl bromide furnished good first-order rate constants only in the presence of added acetate ions. In the absence of acetate ions the acetolysis displayed the same anomalous features as were observed previously in the case of cholesteryl bromide, showing autocatalytic characteristics and proceeding to an equilibrium. In the presence of acetic anhydride the rate was identical with the initial value of the rate for the uncatalysed reaction, which takes place by an irreversible unimolecular heterolysis and leads to the production of cholesta-3 : 5-diene.

As expected, the rates of acetolysis of the *epi*cholesteryl compounds are slower than those of the corresponding cholesteryl compounds; the ratio of the rates of acetolysis of the epimeric toluene-*p*-sulphonates is twice that for the epimeric bromides.

KINETIC studies of the acetolysis of cholesteryl toluene-*p*-sulphonate (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838) and of cholesteryl bromide (Davies, Meecham, and Shoppee, preceding paper) have shown that both reactions involve a unimolecular heterolysis and that the π-electrons of the 5 : 6-double bond influence the kinetic and stereochemical

* Part XX, preceding paper.

course of the reaction. In view of the different configuration of molecules of the corresponding *epi*cholesteryl compounds, it was of interest to make a parallel kinetic study of their acetolysis. The configuration of the A and B rings of *epi*cholesteryl bromide is shown in the Figure. The carbon atoms $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, and $C_{(10)}$ are coplanar and the bromine



atom possesses the axial conformation. It will be seen that the geometry of the system is unfavourable for interaction between the π-electrons of the 5 : 6-double bond and the β-face of $C_{(3)}$. For effective interaction, the π-electron cloud would have to operate over a distance approximately twice that involved in cholesteryl bromide and, in addition, the 4β-hydrogen atom will exert a screening effect. It follows that, by contrast with the cholesteryl compounds, the cation resulting by heterolysis of the bromine atom in *epi*-cholesteryl bromide will not be stabilised, and that the transition state of formation of the cation will therefore also not be stabilised, so that the energy of activation of the heterolysis will be increased and the rate decreased. In brief the 5 : 6-double bond will exert no significant " driving force " on the heterolysis and the *epi*cholesteryl derivatives should undergo acetolysis less readily than the corresponding cholesteryl compounds. Because of the relative instability of the 3α-yl cation its life will be shorter and it will be less likely to encounter an external anion; instead, the axial 4β-hydrogen atom is favourably disposed for elimination as a proton, leading to cholesta-3 : 5-diene. An alternative or competing process involves hydrogen shift from $C_{(4)}$ to $C_{(3)}$ to give the 4α-yl cation in which the positive charge is stabilised by delocalisation over the triad system $C_{(4)}$–$C_{(5)}$–$C_{(6)}$ (Evans and Shoppee, *J.*, 1953, **540**; cf. Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 21, Fig. XVI). The above considerations imply that the acetolysis of *epi*-cholesteryl compounds should involve an irreversible heterolysis as the rate-determining step, the irreversibility arising from the rapid elimination of a proton from, or rearrangement of, the resulting cation.

TABLE 1. *Acetolysis of* epi*cholesteryl toluene*-p-*sulphonate.*

Concn. (10^{-3}M)	Added solute *	10^4k (min.$^{-1}$) (average)	Concn. (10^{-3}M)	Added solute	10^4k (min.$^{-1}$) (average)
	At 50·05°			*At 50·05°*	
1·725	0·0387M-acetate	21·3	1·739	None	15·3
1·737	0·0200M-acetate	19·5	1·731	0·0404M-NaOAc	19·9
1·738	0·0187M-TsO †	20·8	1·737	0·42M-H_2O	20·9
1·736	0·0393M-perchlorate	30·9	1·737	1·0M-Ac_2O	14·4
1·731	0·0176M-perchlorate + 0·0215M-$HClO_4$	23·9		*At 40·25°*	
			1·403	0·25M-H_2O	5·08
			0·881	0·25M-H_2O	5·25
			0·879	None	4·53

* Diphenylguanidinium salts. † TsO = toluene-*p*-sulphonate.

A summary of the results obtained from kinetic measurements on the acetolysis of *epi*cholesteryl toluene-*p*-sulphonate is given in Table 1. The molality given is that of the toluene-*p*-sulphonate. Each run was found to follow a first-order reaction and the specific rate constants, calculated by using the usual first-order rate expression, are also listed.

The increase in the rate in the presence of added acetate ions is of the order of magnitude

expected from an ionic-strength effect in acetic acid. Thus the two-fold increase in the concentration of added diphenylguanidinium acetate only increased the value of the specific rate constant from $19{\cdot}5 \times 10^{-4}$ to $21{\cdot}3 \times 10^{-4}$ min.$^{-1}$. The relatively greater increase in rate observed in the presence of diphenylguanidinium perchlorate may be attributed to the greater degree of dissociation of this solute. A unimolecular mechanism is therefore indicated and the rate-determining step must be the heterolysis of the *epi*-cholesteryl toluene-*p*-sulphonate. Since cholesta-3 : 5-diene forms the main product of acetolysis, the carbonium ion resulting from heterolysis is subsequently stabilised by elimination of a proton at $C_{(4)}$. The specific rate constant in the absence of added acetate ions showed little downward drift with time. Moreover, the addition of a common-ion solute such as diphenylguanidinium toluene-*p*-sulphonate produced no significant retardation of the reaction. These observations are consistent with the irreversibility of the rate-determining step.

Addition of water produced an increase in rate comparable with that observed from an ionic-strength effect. This again confirms the conclusion that the reaction involves an *E*1 mechanism. Increasing the dielectric constant of the solvent will tend to stabilise the charged transition state more than the neutral initial state and thus reduce the activation energy and accelerate the reaction. The reaction was not catalysed by hydrogen ions, and the presence of acetic anhydride led to only a very slight retardation.

The corresponding results obtained for the acetolysis of *epi*cholesteryl bromide in the presence of various solutes are given in Table 2.

In the absence of added acetate ions the acetolysis (Table 3) was found to display the same anomalous features as had been observed earlier for cholesteryl bromide (Davies, Meecham, and Shoppee, *loc. cit.*). The reaction shows autocatalytic characteristics and proceeds to an equilibrium corresponding to ~66% conversion.

Comparison of the initial specific rate constant obtained by extrapolation to zero time ($1{\cdot}07 \times 10^{-4}$ min.$^{-1}$) under these conditions with the specific rate constants given in Table 2.

TABLE 2. *Acetolysis of approx.* 0·02M-epi*cholesteryl bromide at* 94·8° ± 0·2°.

Added solute *	10^4k (min.$^{-1}$) (average)	Added solute	10^4k (min.$^{-1}$) (average)
0·0331M-acetate	1·30	0·0556M-NaOAc	1·51
0·0553M-acetate	1·78	1·0M-Ac_2O	1·07
0·0289M-acetate + 0·01120M-bromide	1·68	1·0M-Ac_2O at 106·6°	3·34
0·0339M-acetate + 0·0208M-perchlorate	2·32		

* Diphenylguanidinium salts.

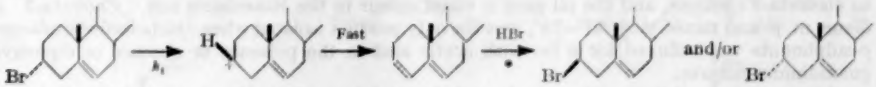
TABLE 3. *Acetolysis of approx.* 0·02M-epi*cholesteryl bromide at* 94·8° ± 0·2°.

Time (min.)	10^2M	Reaction (%)	10^4k (min.$^{-1}$)	Time (min.)	10^2M	Reaction (%)	10^4k (min.$^{-1}$)
240	2·13	3·5	1·50	1440	1·86	56·8	5·83
480	2·00	11·3	2·50	1920	2·02	61·7	4·99
720	2·03	30·3	5·01	2440	2·03	64·1	4·03
960	1·95	48·8	6·98				

shows that, apart from salt effects, the acetolysis of *epi*cholesteryl bromide also involves an *E*1 mechanism. The added salt effect is similar to, but smaller than, that observed for 1-phenylethyl chloride by Steigman and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 2537). A small amount of reaction by an *E*2 mechanism would not be detected by our method, but the low nucleophilic power of the acetate ion renders this improbable. The rate in the presence of acetic anhydride is identical with that of the uncatalysed reaction. This behaviour is similar to that observed for the acetolysis of cholesteryl bromide and lends support to the view that the two reactions involve ionisation as the rate-determining steps. Addition of water to the solvent did not appreciably influence the autocatalysed reaction although at equilibrium the reaction was more complete.

The first four values in Table 3 can be fitted to a kinetic expression of the type that was found to apply to the acetolysis of cholesteryl bromide, but the last three values deviate

from this expression. Since the solutions developed colour as the reaction proceeded, it is unlikely that the titrations effected on solutions maintained at 95° for more than 24 hr. are very reliable. The apparent position of equilibrium is not only significantly less (66%) than that observed for cholesteryl bromide (85%), but is also inconsistent with the observation that addition of hydrogen bromide to cholesta-3 : 5-diene proceeds only to the extent of 10%. The annexed mechanism of reaction appears to account for the facts.



* 1 : 4-Addition to the diene is not excluded by the absorption ($\lambda_{max.}$ 210 mμ) observed.

TABLE 4.

	Cholesteryl toluene-*p*-sulphonate, 10^4k (min.$^{-1}$) at 50°	*epi*Cholesteryl toluene-*p*-sulphonate, 10^4k (min.$^{-1}$) at 50·05°	Cholesteryl bromide, 10^4k (min.$^{-1}$) at 94·8°	*epi*Cholesteryl bromide, 10^4k (min.$^{-1}$) at 94·8°
In presence of acetic acid	79	15·3	2·50	1·07
In presence of sodium acetate	200	19·9	7·0	1·51
E (kcal. mole^{-1})	25·0	25·2	26·5	26·8
$\Delta H^{\ddagger}$ (kcal. mole^{-1})	24·4	24·6	25·8	26·1
$\Delta S^{\ddagger}$ (kcal. mole^{-1} deg.$^{-1}$)	−1·0	−3·7	−13·5	−14·5

The data in Table 4 permit a comparison of the rates of acetolysis of cholesteryl and *epi*cholesteryl compounds. As expected, the rates of acetolysis of the *epi*cholesteryl compounds are slower. The ratio of rates of acetolysis of the toluene-*p*-sulphonates is twice that for the bromides. Acetolysis of the *epi*cholesteryl compounds is less sensitive to changes in the ionic strength of the solvent, as illustrated by the results given for approximately 0·05M-sodium acetate solutions. This observation is consistent with the smaller separation of charges in the transition state for a replacement reaction, compared with that for an elimination reaction. Correlation of the entropies of activation has already been made (Davies, Meecham, and Shoppee, *loc. cit.*).

EXPERIMENTAL.

For general experimental directions see preceding paper; ultra-violet absorption spectra were determined in EtOH on a Unicam S.P. 500 spectrophotometer with corrected scale.

epi*Cholesteryl Bromide and Toluene*-p-*sulphonate.*—The bromide was prepared according to Shoppee and Summers (*J.*, 1952, 1790) and the toluene-*p*-sulphonate by the method of Shoppee and Evans (*loc. cit.*).

The purification procedures for acetic acid, diphenylguanidine, and other reagents have been described by Davies, Meecham, and Shoppee (*loc. cit.*).

Kinetic Measurements.—The rate of acetolysis of *epi*cholesteryl bromide was studied at 94·8° ± 0·2° and at 106° ± 0·2°, the procedure described by Davies, Meecham, and Shoppee (*loc. cit.*) being used. The end-point in the titrations was always approached from the basic side, with crystal-violet as indicator. To obtain reproducible titration readings, it was necessary to match the colour at the end-point with that of a standard. Rate measurements on *epi*cholesteryl toluene-*p*-sulphonate were made at 50·05° ± 0·01° and at 40·25° ± 0·01°. At these lower temperatures, since solvent loss is less significant and also toluene-*p*-sulphonic acid, unlike hydrogen bromide, is non-volatile in acetic acid solution, it was considered unnecessary to adopt the sealed-ampoule technique employed for measurements on the bromide. Instead, for each run, about 100 ml. of a solution of the toluene-*p*-sulphonate were made up by weight in a glass-stoppered flask. After a known weight of solvent had been allowed to attain the temperature of the thermostat, a weighed amount of the *epi*cholesteryl toluene-*p*-sulphonate was added. The flask was then shaken vigorously to ensure rapid dissolution of the solid; 10-ml. portions of the solution were withdrawn at appropriate intervals and the reaction stopped by rapid cooling. A 10-ml. portion from each run was weighed in order to correct for solvent expansion.

In the absence of added base, the solutions developed a brown colour after about 12 hours' immersion in the thermostat. Basic solutions on the other hand only coloured after 48 hr.

Analysis of Reaction Products.—*epi*Cholesteryl toluene-*p*-sulphonate (90 mg.) was dissolved in 10 ml. of 0·04M-diphenylguanidinium acetate solution in acetic acid. After immersion for 2 days in a thermostat at 50°, the solution was poured into water and extracted with benzene. The benzene extract was washed with water, 2N-sodium carbonate, and again with water, dried, and evaporated. An ethanolic solution of the residual oil showed $\lambda_{max.}$ 235 mμ corresponding to cholesta-3 : 5-diene, and the oil gave a violet colour in the Rosenheim test. Cholesta-3 : 5-diene, m. p. and mixed m. p. 77—78°, was the only product isolated when *epi*cholesteryl toluene-*p*-sulphonate was refluxed for 6 hr. with acetic acid in the presence or absence of diphenylguanidinium acetate.

An ampoule containing 48 mg. of *epi*cholesteryl bromide in 5 ml. of a 0·05M-diphenylguanidinium acetate solution in acetic acid was kept in a thermostat at 95° for 73 hr. The brown solution was poured into water and neutralised with sodium carbonate. The ether extract of the steroid products was washed with water, dried, and evaporated. The product, dissolved in pentane, was filtered through a column of aluminium oxide to remove diphenylguanidine present. The ultra-violet absorption spectrum of the resulting oil showed $\lambda_{max.}$ 235 mμ, corresponding to cholesta-3 : 5-diene. The oil gave a positive Beilstein test and so contained unchanged *epi*cholesteryl bromide. Similar results were obtained in the absence of diphenylguanidinium acetate. The ultra-violet absorption spectrum of the products showed, in addition to the maximum at 235 mμ, a slight maximum at 213 mμ, corresponding to an unconjugated Δ^4- or Δ^5-double bond.

A 0·02M-solution with respect to cholesta-3 : 5-diene and hydrogen bromide in acetic acid solution was kept at 106·6° for 7·5 hr. Titration of the remaining hydrogen bromide corresponded to 9·9% reaction. When the reaction was allowed to proceed for 44 hr. a 9·5% conversion was observed. The products gave a positive Beilstein test for bromine and showed a slight absorption maximum at 213 mμ, corresponding to an unconjugated Δ^4- or Δ^5-double bond.

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University of Wales, University College, Swansea. [*Received, September 16th*, 1954.]

Steroids and Walden Inversion. Part XXII. The Configuration of Cholesterylamine.*

By J. H. Pierce, C. W. Shoppee, and G. H. R. Summers.

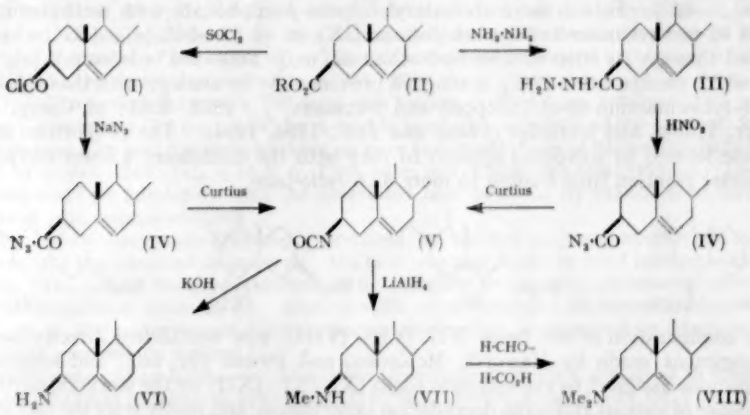
[Reprint Order No. 5739.]

Cholest-5-ene-3β-carboxylic acid (Marker's acid) has been converted into the azide by way of the chloride and by treatment of the hydrazide with nitrous acid. The azide undergoes the Curtius rearrangement to give the *iso*cyanate, which by alkaline hydrolysis affords 3β-aminocholest-5-ene; alternatively, reduction of the *iso*cyanate with lithium aluminium hydride yields 3β-methylaminocholest-5-ene. The configurations of these bases follow from the known configuration of Marker's acid, and the preservation of configuration in the migrating group in the Curtius rearrangement.

In connection with concurrent work it became necessary to establish the configuration at $C_{(3)}$ of cholesterylamine. This primary base, m. p. 98°, was obtained from cholesteryl chloride by treatment with ethanolic ammonia at 100° in the presence of ammonium iodide by Windaus and Adamla (*Ber.*, 1911, **44**, 3051). Subsequently, it was prepared (m. p. 94°, $[\alpha]_D$ −26°) from cholesteryl toluene-*p*-sulphonate by treatment with liquid ammonia at 98° by Julian, Cole, and Magnani (*J. Amer. Chem. Soc.*, 1948, **70**, 1834), and (m. p. 90—91°) by Howarth, McKenna, and Powell (*J.*, 1953, 1110); the British authors

* Part XXI, preceding paper.

also treated cholesteryl toluene-*p*-sulphonate with monomethylamine and with dimethylamine and obtained a 3-methylaminocholest-5-ene, m. p. 113°, and a dimethylamino-analogue, m. p. 152°, $[\alpha]_D$ −32°. We have prepared 3β-aminocholest-5-ene (VI) by the following method :



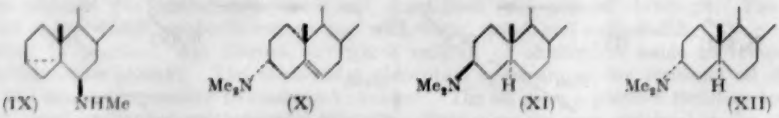
Cholest-5-ene-3β-carboxylic acid (Marker's acid) (II; R = H), in which the β-configuration of the carboxyl group is established (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705; cf. Corey and Sneen, *J. Amer. Chem. Soc.*, 1953, **75**, 6234), was converted into the chloride (I) which by treatment with dry sodium azide in anhydrous acetone–dioxan gave the azide (IV). Alternatively, the methyl ester (II; R = Me) was treated with hydrazine to yield the hydrazide (III), which by treatment with nitrous acid in benzene–acetic acid gave the azide (IV).

The Curtius rearrangement of azides is an intramolecular change in which configuration in the migrating group is preserved, since Kenyon and Young (*J.*, 1941, 263) have converted (+)-hydratropazide into (−)-1-phenylethylamine of over 99% optical purity, whilst Jones and Wallis (*J. Amer. Chem. Soc.*, 1926, **48**, 169) have transformed (+)-α-benzylpropionazide into (−)-1-benzylethylamine which Kenyon, Phillips, and Pitman (*J.*, 1935, 1072) showed to possess the same configuration. The azide (IV) by the Curtius rearrangement furnished the *iso*cyanate (V), m. p. 90—96°; attempts to purify the crude *iso*cyanate by recrystallisation from inert solvents or from acetone–methanol led to the production of high-melting compounds (*s*-dicholest-5-en-3β-ylurea?) and the urethane respectively.

Hydrolysis of the crude crystalline *iso*cyanate (V), prepared by either procedure, with methanolic potassium hydroxide gave after chromatography 3β-aminocholest-5-ene (VI), m. p. 94°, $[\alpha]_D$ −26°; a second compound, m. p. 139—140°, $[\alpha]_D$ −37°, after crystallisation from acetone, was also isolated and was regarded as a polymorph of the base (VI), because by brief treatment with acetic anhydride it was converted into the acetyl derivative of the base (VI), m. p. 238—239°, $[\alpha]_D$ −41° [Windaus and Adamla (*loc. cit.*) report m. p. 238—242°], which by hydrogenation with platinum oxide in acetic acid gave 3β-acetamidocholestane, m. p. 242—243°, $[\alpha]_D$ +11·5°, identical with a sample, m. p. 245°, $[\alpha]_D$ +12°, prepared by reduction of cholestan-3-one oxime with sodium–ethanol according to the procedure of Howarth and Dodgson (*J.*, 1952, 67). Professor R. D. Howarth informed us on September 11th, that the Sheffield group had encountered a compound, m. p. 140°, $[\alpha]_D$ −33°, which is identical with our supposed polymorph; Professor Howarth has further most kindly informed us in a letter of September 30th that the compound is, in fact, the *iso*propylidene derivative of the base (VI), from which it is indistinguishable by elementary analysis.

Reduction of the crude crystalline *iso*cyanate (V) with lithium aluminium hydride gave 3β-aminocholest-5-ene (VII), m. p. 113°, $[\alpha]_D$ −37°, which was identical with a specimen prepared from cholesteryl toluene-*p*-sulphonate by treatment with ethanolic methyl-

amine at 100° according to the directions of Haworth, McKenna, and Powell (*loc. cit.*), and which by methylation with formaldehyde–formic acid gave 3β-dimethylaminocholest-5-ene (VIII), m. p. 151°, $[\alpha]_D$ −32° {Haworth, McKenna, and Powell, *loc. cit.*, give m. p. 151°, $[\alpha]_D$ −31°, whilst Sorm, Labler, and Czerny (*Chem. Listy*, 1953, **47**, 418) give m. p. 151°, $[\alpha]_D$ −32°}. Solvolysis of cholesteryl toluene-*p*-sulphonate with methylamine also afforded 6β-methylamino-3 : 5-*cyclo*cholestane (IX), m. p. 52—54°, $[\alpha]_D$ +27°, which was separated through its ether-soluble hydrochloride, m. p. 260—261° (decomp.), $[\alpha]_D$ +37°, and in which configuration at $C_{(6)}$ is assigned provisionally by analogy with that established for 3 : 5-*cyclo*cholestan-6β-ol (Shoppee and Summers, *J.*, 1952, 3361; cf. Corey, Sneen, Danaher, Young, and Rutledge (*Chem. and Ind.*, 1954, 1294). The proportion of 3 : 5-*cyclo*-base formed by solvolysis appears to vary with the conditions, a lower temperature or a shorter reaction time leading to more 3 : 5-*cyclo*-base.



(IX) (X) (XI) (XII)

The configuration of the bases (VI), (VII), (VIII), now established directly, confirms the assignment made by Haworth, McKenna, and Powell (*loc. cit.*), and supports the configurations assigned to the epimeric bases (X), (XI), (XII) by the workers, partly from the evidence of various Hofmann degradation experiments, and partly from the fact that the more thermodynamically stable equatorial epimerides tend to be produced by reduction of oximes of steroid ketones by use of sodium–ethanol.

Experimental

For general experimental directions see *J.*, 1954, 4224. $[\alpha]_D$ are in $CHCl_3$; Al_2O_3 used was Spence type H, 200 mesh, activity ~II, neutralised when necessary by Reichstein and Shoppee's procedure (*Discuss. Faraday Soc.*, 1949, **7**, 305).

Cholest-5-ene-3β-carboxyhydrazide.—Cholest-5-ene-3β-carboxylic acid (m. p. 222—223°; 1·22 g.) (Roberts, Shoppee, and Summers, *loc. cit.*) was refluxed with hydrazine hydrate (100%; 8 c.c.) in ethanol for 40 hr. Part of the solvent was removed by distillation and the hydrazide separated on cooling; recrystallisation from ethanol gave *cholest-5-ene-3β-carboxyhydrazide* as rectangular plates, m. p. 214—215°, $[\alpha]_D$ −24° (*c*, 1·39) [Found (after drying at 100°/0·01 mm. for 3 hr.): N, 5·8. $C_{28}H_{48}ON_2$ requires N, 6·5%].

Cholest-5-en-3β-yl iso*Cyanate.*—(*a*) The hydrazide (250 mg.) was dissolved in benzene (15 c.c.) and acetic acid (35 c.c.), the solution cooled to 0°, and 2N-hydrochloride acid (0·35 c.c.) added; a solution of sodium nitrite (95 mg.) in water (4 c.c.) was added dropwise and the mixture stirred at 0° for 1·5 hr. The mixture was diluted, and the benzene extract separated, washed with sodium hydrogen carbonate solution, and with water, and refluxed for 1 hr. to ensure complete conversion into the *iso*cyanate; this was obtained by evaporation as a crystalline solid, m. p. 80—96°, which could not be satisfactorily purified by recrystallisation.

(*b*) Cholest-5-ene-3β-carboxylic acid (1·22 g.), dissolved in benzene, was refluxed with thionyl chloride (1·5 c.c.) for 2 hr.; complete evaporation in a vacuum gave the crude chloride, m. p. 110—117°. The chloride, dissolved in *dry* acetone (50 c.c.) and dioxan (25 c.c.; freshly distilled over sodium), was treated dropwise with a solution of sodium azide (430 mg.) in water (3·5 c.c.) with stirring. After 10 min. the mixture was diluted, and the precipitate filtered off, washed with water, and dried in a vacuum-desiccator. The material was extracted with pentane, in which it was completely soluble (absence of original carboxylic acid), and the product obtained by evaporation dissolved in benzene and refluxed for 1 hr. to ensure conversion into the *iso*cyanate; this was obtained by evaporation as a crystalline solid, m. p. 80—90°, undepressed on admixture with the specimen obtained by procedure (*a*).

3β-*Aminocholest-5-ene.*—(i) The crude *iso*cyanate [625 mg. prepared by method (*b*)] was refluxed with 10% ethanolic potassium hydroxide (45 c.c.) for 1·5 hr.; the cooled solution was filtered from insoluble material (282 mg.), m. p. >250°, and evaporated completely. The residue was dissolved in ether, and the base isolated as the insoluble hydrochloride by treatment with dry hydrogen chloride. Basification with 2N-potassium hydroxide, ether-extraction, washing, drying, and evaporation furnished the amine as an oil, which crystallised overnight.

Part of the product by repeated recrystallisation from ether–pentane gave 3β-aminocholest-5-ene (VI), m. p. 89—94°, $[\alpha]_D$ −26° (*c*, 0·9), whilst part was purified by chromatography on a column of aluminium oxide (5 g.). Elution with ether–pentane (1 : 1) removed some non-basic material, whilst use of acetone–ether afforded a crystalline compound; recrystallisation from acetone gave a compound, m. p. 139—140°, $[\alpha]_D$ −37° (*c*, 0·87) [Found (after sublimation at 120°/0·01 mm.): C, 84·0; H, 12·4; N, 3·6%], which we regarded as a polymorph of the base (VI), but which has been shown by Haworth *et al.* (personal communication) to be the *iso*propylidene derivative of the base (VI). The compound was converted by heating with acetic anhydride into the acetyl derivative, m. p. 238—239° (from ether), $[\alpha]_D$ −41° (*c*, 1·01), of the base (VI). The acetyl derivative (90 mg.) was shaken with Adams catalyst (18·5 mg.) in hydrogen; absorption (7·5 c.c.; calc. for 1 double bond and reduction of the catalyst, 8·1 c.c.) was complete in 3 hr. and the usual working up gave hexagonal plates of 3β-acetamidocholestane (68 mg.), m. p. 242—243°, $[\alpha]_D$ +11·5° (*c*, 1·06), after recrystallisation from ethanol. The m. p. was undepressed on admixture with the acetylated base obtained by reduction of cholestan-3-one oxime with sodium–ethanol.

(ii) The crude *iso*cyanate [237 mg.; prepared by method (*a*)] was hydrolysed and the crude base (114 mg.) isolated as under (i); the base was acetylated by brief heating with acetic anhydride (3 c.c.), and the product obtained by complete evaporation chromatographed on a column of aluminium oxide (5 g.). Elution with ether furnished 3β-acetamidocholest-5-ene (80 mg.), m. p. 238°, after recrystallisation from acetone–ether, undepressed on admixture with the specimen prepared by method (i).

3β-*Methylaminocholest-5-ene.*—(*a*) The crude *iso*cyanate (600 mg.), dissolved in ether, was treated with lithium aluminium anhydride (175 mg.), heated under reflux for 1 hr., cooled, and carefully diluted with water. The precipitate of aluminium hydroxide was filtered off, and the base isolated from dry ethereal solution as the hydrochloride, m. p. 222—226° (decomp.), $[\alpha]_D$ −27° (*c*, 1·21), after crystallisation from chloroform–acetone, this salt being basified with 2N-sodium carbonate. The product was chromatographed on aluminium oxide (5 g.); elution with ether–pentane (1 : 1) gave 3β-methylaminocholest-5-ene, m. p. 111—113°, $[\alpha]_D$ −37·5° (*c*, 0·8), after recrystallisation from acetone, undepressed on admixture with the specimen prepared by method (*b*) below.

(*b*) Cholesteryl toluene-*p*-sulphonate (5 g.) and methylamine (5 c.c. of 33% w/w solution in ethanol) were heated in a sealed tube at 100° for 8 hr.; the mixture was evaporated, and the product basified with ethanolic potassium hydroxide, diluted, and extracted with ether. The dry ethereal extract was treated with dry hydrogen chloride, and the precipitate collected and basified to give the amine (250 mg.) which after chromatographic purification (elution with ether–benzene, ether, acetone–ether, and acetone) furnished 3β-methylaminocholest-5-ene (140 mg.), m. p. 113°, as needles, after recrystallisation from acetone; methylation of a specimen (32 mg.) with formaldehyde (0·5 c.c.; 40%), formic acid (0·5 c.c.; 90%), and water (1 c.c.) at 100° for 4 hr. gave 3β-dimethylaminocholest-5-ene, m. p. 151—152°, $[\alpha]_D$ −32° (*c*, 0·76), after recrystallisation from acetone. The ethereal filtrate was evaporated and the residue extracted with pentane to furnish a solid, which by recrystallisation from acetone gave material (770 mg.), m. p. 80—88°, $[\alpha]_D$ −28° (*c*, 1·09), which is possibly 3α-methylaminocholest-5-ene (cf. Haworth, McKenna, and Powell, *loc. cit.*); the residue of ether-soluble hydrochloride gave a crude base (1·12 g.), which was purified by chromatography on aluminium oxide (30 g.) prepared in pentane. Elution with 50 c.c. portions of pentane, benzene–pentane (1 : 1), benzene, ether–benzene (1 : 1), and ether gave fractions of m. p. 52—54° (45 mg.), 52—54° (413 mg.), 51—53° (66 mg.), 47—51° (166 mg.), and 48—52° (90 mg.). Recrystallisation from acetone gave 6β-*methylamino*-3 : 5-cyclo*cholestane*, m. p. 52—54°, $[\alpha]_D$ +27°, +28° (*c*, 0·98, 1·18) [Found (after distillation at 150°/0·01 mm.): C, 83·6; H, 12·2. $C_{28}H_{49}N$ requires C, 84·1; H, 12·4%]; the hydrochloride, obtained by precipitation with hydrogen chloride from pentane solution, crystallised from chloroform–acetone in needles, m. p. 260—261° (decomp.), $[\alpha]_D$ +37° (*c*, 0·78).

One of us (R. H. P.) acknowledges a grant from the Swansea Local Education Authority; we thank Glaxo Laboratories Ltd. for a gift of cholesterol.

UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA [*Received, September 18th,* 1954.]

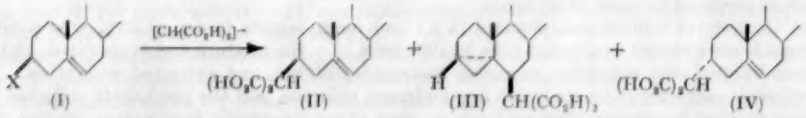
Steroids and Walden Inversion. Part XXIII. The Production of 3α-Substituted Δ⁵-Steroids in Replacement Reactions of 3β-Substituted Δ⁵-Steroids.*

By J. H. Pierce, H. C. Richards, C. W. Shoppee, R. J. Stephenson, and G. H. R. Summers.

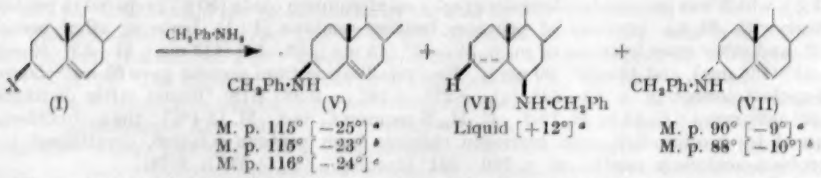
[Reprint Order No. 5788.]

It has been generally thought that replacement reactions at $C_{(3)}$ in 3β-substituted Δ⁵-steroids proceed by a unimolecular heterolysis with complete retention of configuration at $C_{(3)}$ owing to participation of the π-electrons of the 5 : 6-double bond. This view is correct for weak nucleophilic reagents, *e.g.*, OAc^-, but requires modification for more powerful nucleophilic reagents. Six examples are given, with appropriate experimental proof, to show that in media of low dielectric constant and with nucleophiles of sufficient power, the unimolecular heterolysis may be accompanied, or largely superseded, by a bimolecular substitution with inversion of configuration at $C_{(3)}$ in which the π-electrons of the 5 : 6-double bond do not participate.

In 1951, two of us observed that a replacement reaction at $C_{(3)}$ in a 3β-substituted Δ⁵-steroid could lead to a 3α-substituted Δ⁵-steroid; thus the reaction of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with malonate ion in toluene at 110° gives three isomeric products: 3β-cholesterylmalonic acid (II), 3 : 5-*cyclo*cholestan-6β-ylmalonic acid (III), and 3α-cholesterylmalonic acid (IV) (Shoppee and Stephenson, *J.*, 1954, 2230; cf. Kaiser and Svarz, *J. Amer. Chem. Soc.*, 1945, **67**, 1309; 1947, **69**, 846; 1949, **71**, 517).



A second case was reported in 1952. Julian *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1831 : ref. *a*) found that cholesteryl toluene-*p*-sulphonate with benzylamine at 180° gave *N*-benzyl-3β-cholesterylamine (V) and *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine (VI). Vavasour *et al.* (*Canad. J. Chem.*, 1952, **30**, 933 : ref. *b*) by similar treatment of cholesteryl chloride (I; X = Cl) isolated three isomeric amines : two of these products, (V) and (VI), were identical with those obtained by Julian *et al.*; the third was correctly regarded as *N*-benzyl-3α-cholesterylamine (VII).

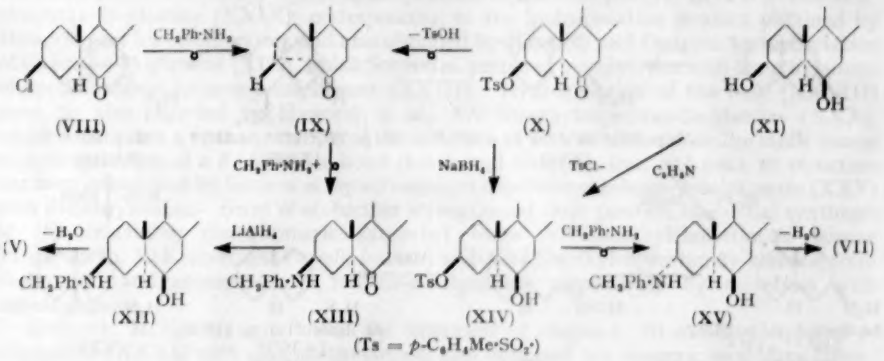


(Figures in square brackets are $[\alpha]_D$. Superscripts refer to references so marked in the text.)

We have confirmed the Canadian work and we have now (ref. *c*) proved the structures of the amines (V) and (VII) by the following partial syntheses. 3β-Chlorocholestan-6-one (VIII) with benzylamine at 180° gives initially 3 : 5-*cyclo*cholestan-6-one (IX); this is cleaved in benzylamine by the benzylammonium cation $[NH_3{\cdot}CH_2Ph]^+$, which functions as an acid, like $[NH_4]^+$ in liquid ammonia (cf. Shoppee and Summers, *J.*, 1952, 1787,

* Part XXII, preceding paper.

3365), to yield *N*-benzyl-6-oxocholestan-3β-ylamine (XIII). This by reduction with lithium aluminium hydride affords *N*-benzyl-6β-hydroxycholestan-3β-ylamine (XII), smoothly dehydrated by phosphorus oxychloride–pyridine at 15° [5α-H(axial)/6β-OH(axial) : *trans*] to give *N*-benzyl-3β-cholesterylamine (V).

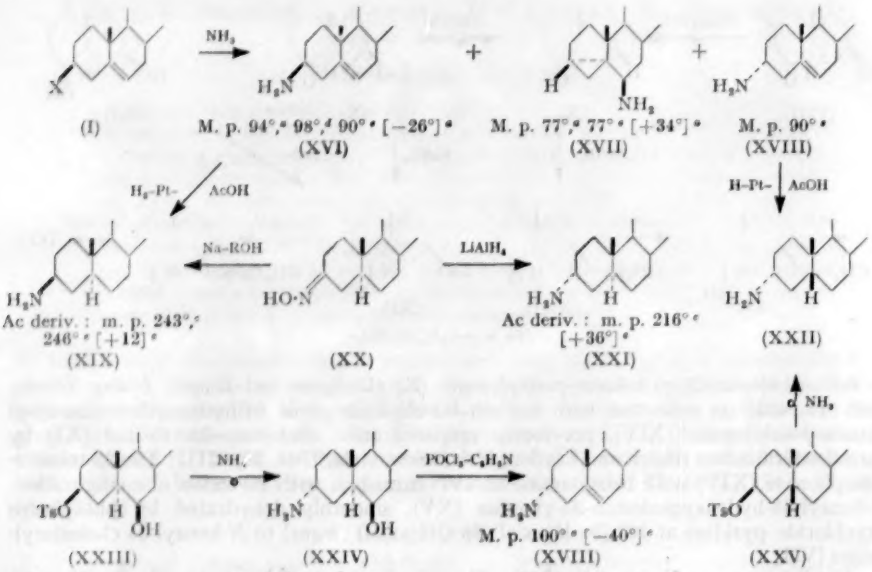


6-Oxocholestan-3β-yl toluene-*p*-sulphonate (X) (Dodgson and Riegel, *J. Org. Chem.*, 1948, **13**, 424) on reduction with sodium borohydride gives 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XIV), previously prepared from cholestane-3β : 6β-diol (XI) by partial esterification (Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 671). The 3β-toluene-*p*-sulphonate (XIV) with benzylamine at 180° furnishes, with inversion of configuration, *N*-benzyl-6β-hydroxycholestan-3α-ylamine (XV), smoothly dehydrated by phosphorus oxychloride–pyridine at 15° [5α-H(axial)/6β-OH(axial) : *trans*] to *N*-benzyl-3α-cholesteryl-amine (VII).

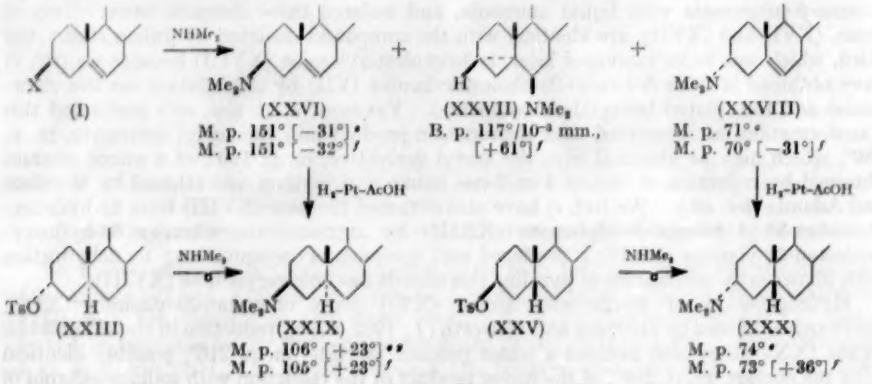
A third case was reported in 1953. The reaction of cholesteryl chloride (I; X = Cl) with ammonia in the presence of ammonium iodide was examined by Windaus and Adamla (*Ber.*, 1911, **44**, 3051 : ref. *d*), who isolated 3β-cholesterylamine (XVI). Julian *et al.* (*loc. cit.* : ref. *a*) later examined the reaction of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with liquid ammonia, and isolated 3β-cholesterylamine (XVI) and 3 : 5-*cyclo*cholestan-6β-ylamine (XVII), which were also obtained from *N*-benzyl-3β-cholesterylamine (V) and *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine (VI) respectively by conversion with hypochlorous acid into the chloramines, dehydrochlorination, and hydrolytic fission of the resulting benzylidene compounds. More recently, Haworth, McKenna, and Powell (*J.*, 1953, 1110 : ref. *e*) re-investigated the reaction of cholesteryl toluene-*p*-sulphonate with liquid ammonia, and isolated three isomeric bases. Two of these, (XVI) and (XVII), are identical with the compounds isolated by Julian *et al.*; the third, which was to be examined later, is 3α-cholesterylamine (XVIII) because we (ref. *c*) have obtained it from *N*-benzyl-3α-cholesterylamine (VII) by degradation *via* the chloramine and the related benzylidene compound. Vavasour *et al.* (*loc. cit.*) performed this transformation but converted their degradation product into the acetyl derivative, m. p. 189°, which may be identical with the acetyl derivative, m. p. 190°, of a minor product obtained by reduction of cholest-4-en-3-one oxime with sodium and ethanol by Windaus and Adamla (*loc. cit.*). We (ref. *c*) have also obtained the base (XVIII) from 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XXIII) by ammonolysis, whereby 6β-hydroxycholestan-3α-ylamine (XXIV) is produced with inversion of configuration; by dehydration with phosphorus oxychloride in pyridine this affords 3α-cholesterylamine (XVIII).

Hydrogenation of 3β-cholesterylamine (XVI) gives cholestan-3β-ylamine (XIX), previously obtained by Dodgson and Haworth (*J.*, 1952, 67) by reduction of cholestan-3-one oxime (XX); they also isolated a minor product [acetate, m. p. 216°, possibly identical with the acetate, m. p. 216°, of the major product of the reduction with sodium–ethanol of cholest-4-en-3-one oxime (Windaus and Adamla, *loc. cit.*)], which is cholestan-3α-ylamine

(XXI) since we have obtained it from the oxime (XX) by reduction with lithium aluminium hydride. It is of interest here that hydrogenation of 3α-cholesterylamine (XVIII) gives mainly coprostan-3α-ylamine (XVII) (cf. Lewis and Shoppee, *Chem. and Ind.*, 1953, 897, 933), also obtainable by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate (XXV) (Richards, Shoppee, and Summers, unpublished work).



A fourth case was also reported in 1953. Haworth, McKenna, and Powell (*loc. cit.*) by treatment of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with dimethylamine isolated *N*-benzyl-3β-cholesterylamine (XXVI), previously obtained from cholesteryl chloride (I; X = Cl) by Dodgson and Haworth (*loc. cit.*), and an isomeric base later (personal communication) identified as *NN*-dimethyl-3α-cholesterylamine (XXVIII). Sorm, Labler, and Czerny (*Chem. Listy*, 1953, **47**, 418) have also investigated the reaction and have isolated three isomeric bases; two of these products, (XXVI) and (XXVIII), are identical with those of Haworth *et al.*, whilst the the third is *NN*-dimethyl-3 : 5-*cyclo*-cholestan-6β-ylamine (XXVII).



[*e* = Haworth *et al.*; *f* = Sorm *et al.*; *g* = Haworth and Dodgson (*loc. cit.*).]

For some reason, possibly because of unfamiliarity with the S_N2 orientation rule (Ingold, "Structure and Mechanism in Organic Chemistry, George Bell and Sons, London, 1953, p. 377), Sorm *et al.* preferred not to assign configuration at $C_{(3)}$ * to the unsaturated products (XXVI) and (XXVIII), although by partial syntheses of their reduction products they were in a position to do so. Thus hydrogenation of the base (XXVI) gave *NN*-dimethylcholestan-3β-ylamine (XXIX), corresponding to the hydrogenation product obtained by Haworth and his collaborators and also obtained by Haworth and Dodgson by methylation of cholestan-3β-ylamine (XIX), which Sorm *et al.* prepared by solvolysis with dimethylamine of *epi*cholestanyl toluene-*p*-sulphonate (XXIII). Hydrogenation of the base (XXVIII) gave, as also recorded by Haworth *et al.*, *NN*-dimethylcoprostan-3α-ylamine (XXX), which constitutes a further example of the influence of a 3α-substituent on the steric course of hydrogenation of a 5 : 6-double bond (Lewis and Shoppee, *locc. cit.*) since its structure has been established by Sorm *et al.* by solvolysis of coprostanyl toluene-*p*-sulphonate (XXV) with dimethylamine. Sorm *et al.* further strengthened their position by partial syntheses of the remaining stereoisomeric saturated bases *NN*-dimethylcholestan-3α-ylamine (cf. Haworth, McKenna, and Powell, *loc. cit.*) and *NN*-dimethylcoprostan-3β-ylamine from cholestanyl and *epi*coprostanyl toluene-*p*-sulphonate respectively by solvolysis with dimethylamine.

Haworth, McKenna, and Powell, by treatment of pregna-5 : 20-dien-3β-yl toluene-*p*-sulphonate (XXXI) with monomethylamine, also obtained two isomeric secondary bases; one is *N*-methylpregna-5 : 20-dien-3β-ylamine (XXXII), which was identified by methylation and hydrogenation to *NN*-dimethyl*allo*pregnan-3β-ylamine (XXXV), prepared by reduction of *allo*pregnan-3-one oxime (XXXIV) with sodium and amyl alcohol and then methylation; the other is *N*-methylpregna-5 : 20-dien-3α-ylamine (XXXIII), although Haworth *et al.* suggested that it might be *N*-methyl-3 : 5-*cyclo*pregn-20-en-6ξ-ylamine because it was stable to oxidation with potassium iodate in 2N-sulphuric acid, and on account of its conversion by successive methylation and hydrogenation into a tertiary base, $C_{23}H_{41}N$, m. p. 79° (XXXVI), of unknown structure, which was different from *NN*-dimethyl*allo*pregnan-3β- (XXXV) and -3α-ylamine (XXXIX).†

Haworth, McKenna, and Powell made the notable observation that solvolysis of pregn-5-en-3β-yl toluene-*p*-sulphonate (XXXVII) with dimethylamine furnished only a *single* product, m. p. 130°, which gave a negative iodate reaction and by hydrogenation afforded the base (XXXVI); they suggested that this product must have a structure analogous to that of the base (XXXIII).‡ We have proved the structure of the product, m. p. 130°, to be *NN*-dimethylpregn-5-en-3α-ylamine (XXXVIII), so that here substitution (XXXVII ⟶ XXXVIII) proceeds with substantially complete inversion of configuration.

Kishner–Wolff reduction of pregnenolone (XL) gave pregn-5-en-3β-ol (XLI), which by

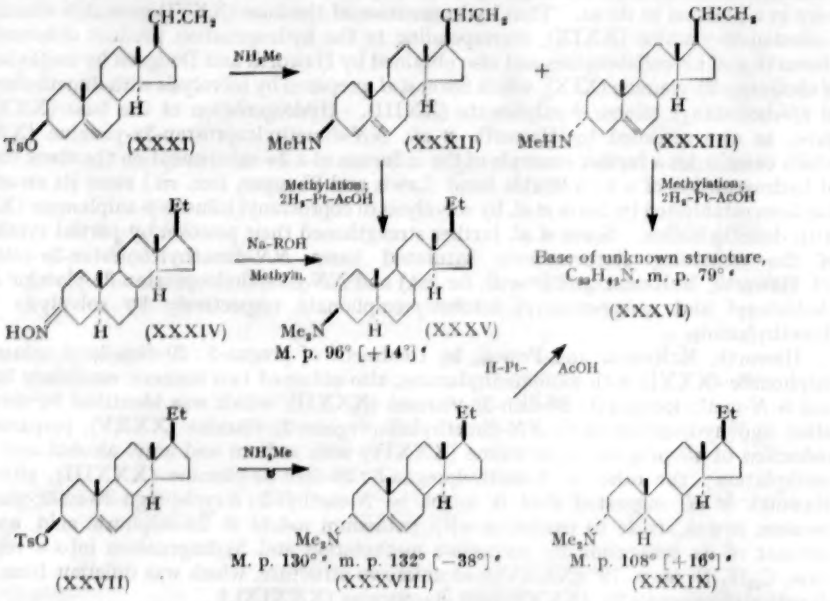
* Sorm *et al.* state (*loc. cit.*, p. 420, last paragraph): "We no not ascribe to any of the 3-dimethylamino-steroid derivatives, prepared by us, a definite configuration of the dimethylamino-group at $C_{(3)}$, because neither in the case of these bases, nor in that of the 3-amino-steroid derivatives that have been described earlier, has there been so far any definite proof concerning configuration." Accordingly they use the symbol ξ throughout their paper.

Haworth, McKenna, and Powell (*loc. cit.*) described various Hofmann degradations. The 3β-(equatorial)-configuration of the substituent group in the related primary (XIX), secondary, and tertiary (XXVI) bases can be deduced from the resistance to Hofmann degradation of the quaternary hydroxide derived from the tertiary base (XXIX) as compared with the relatively ready decomposition of *NNN*-trimethylcholestan-3α-ylammonium hydroxide (3α-substituent : axial). The discovery by Lewis and Shoppee (*locc. cit.*) that hydrogenation of 3α-substituted cholest-5-enes leads predominantly to coprostane derivatives enables a parallel deduction to be made of the 3α(equatorial)-configuration of the substituent group in the related secondary and tertiary (XXVIII) bases, since the quaternary hydroxide derived from the tertiary base (XXX) resisted Hofmann degradation.

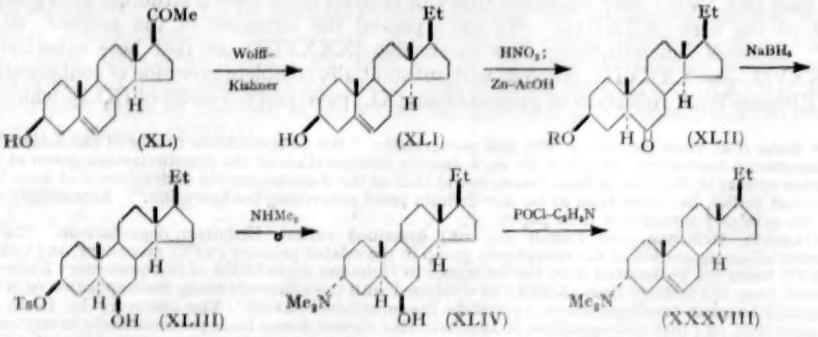
† 3 : 5-*cyclo*Cholestan-6β-ylamine is stable to acidic iodate (Haworth, McKenna, and Powell, *loc. cit.*, p. 1111), but we find that this is also the case for 3α-amino-Δ^5-steroids in contrast to 3β-amino-Δ^5-steroids, which are readily oxidised.

‡ During a personal discussion at Ashburne Hall, Manchester, on March 31st, 1954, Dr. McKenna informed the senior author that the Sheffield University group had modified their earlier view as to the 3 : 5-*cyclo*-structure of this base and that it was now regarded as the 3α-amine (XXXIII). A copy of the MS. of this paper was sent on August 17th, 1954, to Professor R. D. Haworth; in a letter of September 8th, 1954, Professor Haworth and Dr. McKenna informed us that further work, which will be communicated shortly, has shown that the bases, previously regarded as 3 : 5-*cyclo*pregnanes, are in fact the 3α-substituted pregn-5-enes (XXXIII) and (XXXVIII) respectively.

successive nitration and reduction with zinc–acetic acid yielded 6-oxo*allo*pregnan-3β-ol (XLII; R = H); the toluene-*p*-sulphonate of this, on reduction with sodium borohydride, furnished 6β-hydroxy-3β-toluene-*p*-sulphonyloxy*allo*pregnane (XLIII), which by solvolysis

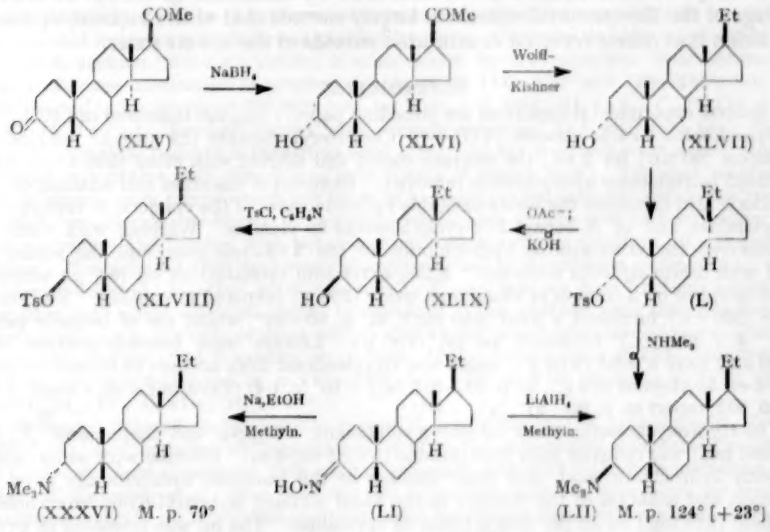


with dimethylamine furnished with inversion of configuration 6β-hydroxy-*NN*-dimethyl*allo*-pregnan-3α-ylamine (XLIV), smoothly dehydrated by phosphorus oxychloride–pyridine at 20° to *NN*-dimethylpregn-5-en-3α-ylamine (XXXVIII).



In an attempt to ascertain the structure of the base (XXXVI), we have prepared *NN*-dimethylpregnan-3α- and -3β-ylamine by the following methods. Pregnane-3 : 20-dione (XLV) was converted by differential reduction with sodium borohydride into 3α-hydroxypregnan-20-one (XLVI) (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, **1953**, **75**, 1286), which by Wolff–Kishner reduction gave pregnan-3α-ol (XLVII). This alcohol was converted into the toluene-*p*-sulphonate (L), a portion of which by solvolysis with dimethylamine gave with inversion of configuration *NN*-dimethylpregnan-3β-ylamine (LII). We have also obtained this base, m. p. 124°, from pregnan-3-one oxime (LI) by reduction with lithium aluminium hydride and methylation of the

primary base; when the oxime (LI) was reduced, however, with sodium–ethanol and the resulting primary base methylated,* we obtained the base, m. p. 79°, (XXXVI), which is therefore *NN*-dimethylpregnan-3α-ylamine. The hydrogenations (XXXIII ⟶ XXXVI) and (XXXVIII ⟶ XXXVI) thus afford further examples of the influence of a 3α-substituent on the stereochemical course of reduction of a 5 : 6-double bond (Lewis and Shoppee, *locc. cit.*).



The residue of the toluene-*p*-sulphonate (L) was subjected to successive acetolysis and alkaline hydrolysis to yield a mixture of pregn-2- and pregn-3-enes accompanied by pregnan-3β-ol (XLIX); this alcohol was converted into the toluene-*p*-sulphonate (XLVIII), which was heated with dimethylamine. Unexpectedly, the product was a base, $C_{22}H_{41}N$, m. p. 142°, for which we are unable to suggest a structure. It is clearly different from the isomeric bases (XXXVI) and (LII); it may be a polymorphic form of the base (XXXVI), although we have so far been unable to convert this into the compound, m. p. 142°.

Configurational studies (Shoppee, *J.*, 1946, 1138) and kinetic investigations (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 475; Pearson, King, and Langer, *J. Amer. Chem. Soc.*, 1951, **73**, 4149; Davies, Meecham, and Shoppee, *J.*, 1955, 679) have led to the view that replacement reactions at $C_{(3)}$ in 3β-substituted Δ^5-steroids occur through a unimolecular heterolysis, giving rise to a carbonium ion, whose configuration (sp^3-hybridisation with a vacant orbital) is preserved by interaction with the π-electrons of the 5 : 6-double bond and which (with appropriate rehybridisation) can react in three ways: (*a*) by union with an external anion and with retention of configuration at $C_{(3)}$, (*b*) by rearrangement with inversion at $C_{(3)}$ to give a 6β-substituted 3 : 5-*cyclo*steroid, and (*c*) by internal depolarisation with ejection of a proton to give a 3 : 5-diene. It now appears that in 3β-substituted Δ^5-steroids, under appropriate conditions, *e.g.*, in media of low dielectric constant, and with nucleophiles of sufficient power, the unimolecular heterolysis leading to the sequelæ (*a*), (*b*), or (*c*) may be accompanied, or even largely superseded, by a bimolecular substitution † with inversion of configuration at $C_{(3)}$ in which the π-electrons of the 5 : 6-double bond do not participate.

This S_N2 process provides a new method for the preparation of 3α-substituted Δ^5-steroids

* Professor R. D. Haworth and Dr. McKenna inform us that they have also obtained the base of m. p. 79° by this proceedure.

† S_N2 replacement in homoallylic systems has recently been envisaged as a competing reaction path by Winstein and Simonetta (*J. Amer. Chem. Soc.*, 1954, **76**, 21; formula XV) but without stereochemical implications.

from their 3β-analogues, which is particularly useful when the entering group is a strong nucleophile, such as an organic base which acts also as the medium for the reaction (3β-substituent *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$, Hal; resulting 3α-substituent = NH_2, NHR, NR_2). Whilst 3α-substituted A/B-*trans* saturated and Δ^5-steroids are accessible from their 3β-analogues by epimerisation, the yields are relatively poor both for covalently unsaturated groups (*e.g.*, CO_2Me, CO_2H, $CO{\cdot}NH_2$, COMe, CN) and for co-ordinatively unsaturated groups (*e.g.*, OH), because the position of equilibrium is controlled by molecular geometry whereby the percentage of the 3β(equatorial)-epimeride largely exceeds that of the 3α(axial)-epimeride; the situation is of course reversed in saturated steroids of the A/B-*cis*-series.

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are measured in $CHCl_3$.

N-Benzylcholest-5-en-3α-ylamine (VII).—(i) Cholesteryl chloride (29 g.) was refluxed with benzylamine (60 c.c.) for 2 hr., the mixture cooled and diluted with ether (500 c.c.), and the precipitated benzylamine hydrochloride removed. Removal of the ether and addition of dilute hydrochloric acid furnished the water-insoluble hydrochlorides of the epimeric *N*-benzylcholest-5-en-3-ylamines and of *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine. Washing with water and ether removed the ether-soluble hydrochloride of the 3 : 5-*cyclo*-base, and the residue was basified with dilute aqueous ammonia. Ether-extraction furnished an oil (9·7 g.) which was chromatographed on a column of aluminium oxide (250 g.) prepared in pentane. Elution with pentane (200 c.c.) furnished a solid (650 mg.), m. p. 60—68°, whilst use of benzene–pentane (1 : 19; 4 × 200 c.c.) furnished an oil (1·8 g.). Elution with benzene–pentane (1 : 1; 8 × 100 c.c.) gave a solid (4·06 g.), which was recrystallised from acetone to furnish *N*-benzylcholest-5-en-3α-ylamine (3·2 g.), m. p. 88—90°, $[\alpha]_D$ −10° (*c*, 1·4) (Vavasour *et al.*, *Canad. J. Res.*, 1952, **30**, 933, report m. p. 90—91°, $[\alpha]_D$ −9°).

(ii) 6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (Shoppee and Stephenson, *J.*, 1954, 2230) (550 mg.) was refluxed with benzylamine (5 c.c.) for 2 hr. Dilution with water, acidification with hydrochloric acid, and ether-washing of the insoluble hydrochloride gave, after basification and isolation of the product in the usual manner, *N*-benzyl-6β-hydroxycholestan-3α-ylamine (280 mg.) as an oil, which failed to crystallise. The oil was dissolved in pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) added at 15°. After 1 hr. the solution was diluted with water, made alkaline with 2N-potassium hydroxide, and extracted with ether. Drying and removal of solvents gave a product, which was filtered through a column of aluminium oxide in benzene–pentane (1 : 1), and crystallised from ethanol to furnish *N*-benzylcholest-5-en-3α-ylamine, m. p. 88—90°, identical with material obtained in the previous preparation.

N-Benzyl-6-oxocholestan-3β-ylamine (XIII).—(i) 3β-Chlorocholestan-6-one (5 g.) was refluxed with benzylamine (25 c.c.) for 2 hr. Dilution with ether and removal of the precipitated benzylamine hydrochloride furnished a filtrate, which after removal of ether and dilution with water gave a solid; this was recrystallised from ethanol to yield *N-benzyl-6-oxocholestan-3β-ylamine* (2·4 g.), m. p. 158°, $[\alpha]_D$ −9° (*c*, 1·3) [Found (after sublimation at 160°/0·005 mm.): C, 82·7; H, 10·8. $C_{34}H_{53}ON$ requires C, 83·0; H, 10·7%].

(ii) 3 : 5-*cyclo*Cholestan-6-one (1 g.) and benzylamine hydrochloride (250 mg.) were refluxed with benzylamine (10 c.c.) for 2 hr. Dilution with water and acidification with hydrochloric acid furnished a precipitate which was removed, dissolved in ethanol, and basified by addition of N-ethanolic potassium hydroxide. Dilution with water, followed by ether-extraction, gave, after removal of solvent and crystallisation from ethanol, *N*-benzyl-6-oxocholestan-3β-ylamine, m. p. 158°, identical with the material obtained in the previous preparation. Refluxing of 3 : 5-*cyclo*cholestan-6-one with benzylamine in the absence of benzylamine hydrochloride resulted in quantitative recovery of the starting material.

N-Benzyl-6β-hydroxycholestan-3β-ylamine (XII).—*N*-Benzyl-6-oxocholestan-3β-ylamine (2 g.) in ether (50 c.c.) was treated at 15° with a solution of lithium aluminium hydride (2 g.) in ether (50 c.c.) for 30 min. Excess of lithium aluminium hydride was decomposed by the addition of water; 50% aqueous potassium hydroxide (50 c.c.) was added and the product extracted with ether. Drying and removal of solvent furnished *N-benzyl-6β-hydroxycholestan-3β-ylamine* (1·5 g.), which, crystallised from ether–acetone, had m. p. 178°, $[\alpha]_D$ +7° (*c*, 2·2) [Found (after sublimation at 200°/0·005 mm.): C, 83·0; H, 11·1; N, 2·5. $C_{34}H_{55}ON$ requires C, 82·7; H, 11·2; N, 2·8%].

N-Benzylcholest-5-en-3β-ylamine (V).—*N*-Benzyl-6β-hydroxycholestan-3β-ylamine (1 g.) was treated in pyridine with phosphorus oxychloride (2 c.c.) at 10°. After 2 hr. at 15° water was

added, and the precipitated solid removed, dissolved in ether, and washed with 2N-potassium hydroxide. Drying and removal of solvent furnished *N*-benzylcholest-5-en-3β-ylamine (760 mg.), m. p. 116—117°, $[\alpha]_D$ −24° (*c*, 1·1), after crystallisation from ethanol (Julian *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1834, report m. p. 116°).

Cholest-5-en-3α-ylamine (XVIII).—(i) 6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (850 mg.) and liquid ammonia (50 c.c.) were heated in a stainless-steel autoclave at 100° for 18 hr., then cooled to 15°. Excess of ammonia was allowed to evaporate, and the brown solid product (810 mg.) collected; an ether–chloroform solution of the product was washed with water, dried, and evaporated to give a gel which was purified by chromatography on aluminium oxide (7 g.). Elution with acetone (200 c.c.) yielded a solid, which by crystallisation from acetone gave *6β-hydroxycholestan-3α-ylamine* as needles, double m. p. 114—115° and 160—162°, $[\alpha]_D$ +19° (*c*, 1·04) [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 80·2; H, 12·3. $C_{27}H_{49}ON$ requires C, 80·3; H, 12·2%]. Further elution with acetone–methanol and methanol gave material difficult to crystallise because it tended to form a gel; all the fractions were united (450 mg.) and treated in pyridine with phosphorus oxychloride (5 drops) at 0°. The dark solution was allowed to attain room temperature, left for 0·25 hr., and poured into ice-cold 2N-hydrochloric acid; the hydrochloride was filtered off, washed with 2N-hydrochloric acid and with water, dried (porous porcelain), and basified with potassium hydroxide, and the resultant oil was extracted with ether. The product (220 mg.) was chromatographed on aluminium oxide (5 g.); elution with benzene–ether (1 : 1), ether, ether–acetone (1 : 1), and acetone gave fractions which failed to crystallise, and whose solutions tended to discolour. The fractions were therefore combined and acetylated with acetic anhydride at 100° to give a solid, which after several recrystallisations from acetone–pentane yielded needles, m. p. 180—186°. Sublimation at 120—130°/0·02 mm. gave 3α-acetamidocholest-5-ene, m. p. 187—189°, $[\alpha]_D$ −30° (*c*, 0·89) (Found: C, 81·2; H, 11·7. Calc. for $C_{29}H_{49}ON$: C, 81·4; H, 11·55%).

(ii) *N*-Benzylcholest-5-en-3α-ylamine, prepared according to the procedure of Vavasour *et al.* (*loc. cit.*), was degraded by hypochlorous acid to the chloramine, dehydrochlorination to afford the benzylidene compound with sodium ethoxide, and acid hydrolysis according to the directions of Vavasour *et al.* The base did not crystallise, and was acetylated by treatment with acetic anhydride at 100°; the resultant solid by recrystallisation from acetone–pentane and sublimation at 120—130°/0·02 mm. gave 3α-acetamidocholest-5-ene, m. p. and mixed m. p. 189°; Vavasour *et al.* record m. p. 189°.

The amide by hydrolysis with 2N-hydrochloric acid under nitrogen and appropriate working up gave *cholest-5-en-3α-ylamine*, m. p. 90° after crystallisation from pentane, raised to 100° on sublimation at 120°/0·02 mm., $[\alpha]_D$ −40° (*c*, 0·89) (Found: C, 84·0; H, 12·4. $C_{27}H_{47}N$ requires C, 84·1; H, 12·3%). The base, with acetic anhydride, regenerated the acetyl derivative, m. p. 189° after crystallisation from acetone–pentane, and by methylation with formaldehyde–formic acid gave after chromatography of the reaction product, *NN*-dimethylcholest-5-en-3α-ylamine (XXVIII), m. p. 70°, $[\alpha]_D$ −29° (*c*, 0·5) after crystallisation from acetone–pentane (cf. refs. *e* and *f*, pp. 695, 696).

Pregn-5-en-3β-ol (m. p. 134°) was prepared from 3β-hydroxypregn-5-en-20-one in 88% yield by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1949, **71**, 3301) and acetylated to furnish 3β-acetoxypregn-5-ene, m. p. 149—150°, $[\alpha]_D$ −60° (*c*, 2·3).

6-Nitropregn-5-en-3β-yl Acetate.—Nitration in ether with fuming nitric acid according to Anagnostopoulos and Fieser's method (*J. Amer. Chem. Soc.*, 1954, **76**, 532) gave mainly unchanged starting material. Pregn-5-en-3β-yl acetate (850 mg.) was therefore dissolved in glacial acetic acid (50 c.c.), and fuming nitric acid (8 c.c.) added with external cooling. After 30 min., water was added, and the precipitated solid washed, dried, and crystallised from methanol to furnish the *6-nitro-compound* as needles, m. p. 136°, $[\alpha]_D$ −91° (*c*, 1·4) [Found (after drying at 60°/0·005 mm. for 12 hr.): C, 70·9; H, 9·2. $C_{23}H_{35}O_4N$ requires C, 70·9; H, 9·1%].

6-Oxoallopregnane-3β-yl Acetate (XLII; R = Ac).—6-Nitropregn-5-en-3β-yl acetate (2 g.) was dissolved in 90% acetic acid (50 c.c.); zinc dust (5 g.) was added during 30 min. to the refluxing mixture. After a total reflux period of 3 hr. the solution was decanted, the zinc dust was extracted with hot acetic acid, and the combined extracts were cooled and diluted with water to furnish a solid, which after washing and drying crystallised from methanol to furnish *6-oxoallopregnan-3β-yl acetate* (1·24 g.), m. p. 173—174°, $[\alpha]_D$ −24·5° (*c*, 1·2) [Found (after sublimation at 160°/0·005 mm.): C, 76·2; H, 10·0. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%].

6-Oxoallopregnan-3β-ol (XLII; R = H).—The foregoing acetate (1·2 g.) was refluxed with N-methanolic potassium hydroxide for 1 hr., the solution diluted with water, and the product extracted with ether to yield, after washing, drying, and removal of solvent and crystallisation

from methanol, 6-*oxoallopregnan*-3β-*ol* (1·05 g.) as plates, m. p. 165°, $[\alpha]_D$ −13° (*c*, 1·1) [Found (after sublimation at 140°/0·005 mm.): C, 78·9; H, 11·1. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%].

6-*Oxoallopregnan*-3β-*yl Toluene*-p-*sulphonate* (XLII; R = *p*-$C_6H_4Me{\cdot}SO_2$).—6-Oxo*allo*pregnan-3β-ol (750 mg.) (dried by azeotropic distillation with benzene) was treated in pyridine (4 c.c.) at 25° with toluene-*p*-sulphonyl chloride (750 mg.) for 8 hr. Dilution with water gave, after the usual washing and drying, 6-*oxoallopregnan*-3β-*yl toluene*-p-*sulphonate* (505 mg.), m. p. 157—158°, $[\alpha]_D$ −9° (*c*, 1·1), after 3 crystallisations from ether [Found (after drying at 60°/0·005 mm. for 12 hr.; C, 71·1; H, 8·6. $C_{28}H_{40}O_4S$ requires C, 71·2; H, 8·5%].

6β-*Hydroxy*allo*pregnan*-3β-*yl Toluene*-p-*sulphonate* (XLIII).—6-Oxo*allo*pregnan-3β-yl toluene-*p*-sulphonate (500 mg.), dissolved in dioxan (10 c.c.) and methanol (20 c.c.), was treated with a solution of sodium borohydride (50 mg.) in water (0·1 c.c.) and methanol (2 c.c.) at 15° for 2 hr. Dilution with water, filtration, washing, and drying gave 6β-*hydroxy*allo*pregnan*-3β-*yl toluene*-p-*sulphonate* (460 mg.) which, crystallised from ether–pentane, had double m. p. 143° and 151°, $[\alpha]_D$ −11·5° (*c*, 1·4) [Found (after drying at 60°/0·005 mm. for 12 hr.): C, 70·6; H, 8·9. $C_{28}H_{42}O_4S$ requires C, 70·9; H, 8·9%].

6β-*Hydroxy*-NN-*dimethyl*allo*pregnan*-3α-*ylamine* (XLIV).—6β-Hydroxy*allo*pregnan-3β-yl toluene-*p*-sulphonate (XLIII) (400 mg.) was heated in a sealed tube at 110° with dimethylamine (10 c.c. of 33% w/w solution) for 5 hr. Evaporation, dilution with ether and N-hydrochloric acid, and addition of potassium hydroxide to the aqueous hydrochloride solution precipitated the base, which was extracted with ether from its strongly alkaline suspension, and then dried. The ether was removed (washing of the ether-extracts to neutrality results in loss of slightly water-soluble base). Crystallisation from 70% methanol gave 6β-*hydroxy*-NN-*dimethyl*allo-*pregnan*-3α-*ylamine* as plates, m. p. 142—150°, raised after sublimation to 145—152°, $[\alpha]_D$ +14° (*c*, 0·8) (yield, 136 mg.) [Found (after sublimation at 140°/0·005 mm.): C, 79·4; H, 11·7. $C_{23}H_{41}ON$ requires C, 79·5; H, 11·9%].

NN-*Dimethylpregn*-5-*en*-3α-*ylamine* (XXXVIII).—6β-Hydroxy-*NN*-dimethyl*allo*pregnan-3α-ylamine (90 mg.) in pyridine (0·5 c.c.) was treated with phosphorus oxychloride (0·2 c.c.) at 15° for 2·5 hr. Dilution with water furnished a precipitate which was filtered off and dissolved in N-ethanolic potassium hydroxide (5 c.c.). Dilution with water furnished a solid, which by recrystallisation from acetone furnished *NN*-dimethylpregn-5-en-3α-ylamine, m. p. 131—132° (after sublimation, m. p. 135°), giving no depression on admixture with a specimen, m. p. 130°, kindly supplied by Professor R. D. Haworth, $[\alpha]_D$ −37·5° (*c*, 1·1) [Found (after sublimation at 150°/0·005 mm.): C, 83·8; H, 11·6. $C_{23}H_{39}N$ requires C, 83·8; H, 11·9%].

Pregnan-3α-*ol*.—3α-Hydroxypregnan-20-one (1·5 g.) (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1286) was refluxed in diethylene glycol (50 c.c.) with sodium hydroxide (2·5 g.) and hydrazine (0·75 c.c.) for 30 min.; the reflux temperature was allowed to rise to 200° and refluxing continued for 2 hr. Dilution with water gave a solid which was dried and chromatographed on aluminium oxide (45 g.). Benzene–pentane (1 : 9 and 1 : 4; each 150 c.c.) gave an oil (20 mg.) whilst use of benzene–pentane (3 : 7; 1 × 150 c.c. and 2 : 3; 2 × 150 c.c.) gave a solid (1·24 g.), which after several crystallisations from methanol furnished pregnan-3α-ol, m. p. 144—146° (Marker and Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 2938, report m. p. 148°). Further elution with benzene gave oils.

Pregnan-3α-*yl Toluene*-p-*sulphonate*.—Pregnan-3α-ol (950 mg.) was dissolved in pyridine (5 c.c.), with toluene-*p*-sulphonyl chloride (1 g.) added. After 20 hr. at 20°, water was added, and the precipitated solid *ester* filtered off, washed, dried, and crystallised from acetone; it had m. p. 132—134° $[\alpha]_D$ +43° (*c*, 1·1) (yield 990 mg.) [Found (after drying at 60°/0·005 mm. for 3 hr.): C, 73·3; H, 9·2. $C_{28}H_{42}O_3S$ requires C, 73·3; H, 9·2%].

Pregnan-3β-*ol*.—The foregoing ester (500 mg.) was heated at 100° for 3 hr. in acetic acid (15 c.c.) with fused potassium acetate (5 g.). Dilution with water and isolation of the product in the usual manner afforded an oil which was refluxed in N-methanolic potassium hydroxide (10 c.c.) for 1 hr., then diluted with water, and the product was extracted with ether. Drying and removal of solvent gave an oil which was chromatographed on a column of aluminium oxide (12 g.). Pentane (100 c.c.) gave a solid (125 mg.) which even after several crystallisations melted over the range 54—78° and had $[\alpha]_D$ +18° (*c*, 2·3) [Found (after sublimation at 120°/0·005 mm.): C, 88·4; H, 12·2. Calc. for $C_{21}H_{34}$: C, 88·0; H, 12·0%]; hydrogenation of the mixture of Δ^3- and Δ^5-pregnene (20 mg.) in ethyl acetate (5 c.c.) in the presence of platinum oxide (10 mg.) gave pregnane, m. p. 78—80°, identical with an authentic specimen kindly supplied by Professor Reichstein. Use of ether as eluant then gave a solid (193 mg.) which after two crystallisations from methanol gave pregnan-3β-ol, m. p. 141—144°, giving a depression of m. p. on admixture with pregnan-3α-ol (Marker and Lawson, *loc. cit.*, report m. p. 144°).

*Pregnan-3β-yl Toluene-*p*-sulphonate.*—Pregnan-3β-ol (120 mg.) in pyridine (1 c.c.) was treated with toluene-*p*-sulphonyl chloride (150 mg.) at 20°. After 12 hr. water was added, and the precipitated solid filtered off, washed and dried to furnish the 3β-*toluene*-p-*sulphonate*, m. p. 98—101°, $[\alpha]_D$ +23° (*c*, 1·0) (yield 105 mg.) [Found (after drying at 60°/0·005 mm. for 3 hr.): C, 73·5; H, 9·8. $C_{35}H_{52}O_3S$ requires C, 73·3; H, 9·2%].

NN-*Dimethylpregnan-3β-ylamine.*—(*a*) The foregoing ester (300 mg.) was heated in a sealed tube at 110° for 5 hr. with dimethylamine (7 c.c.; 33% w/w). Evaporation of the excess of dimethylamine, dilution with ether, and precipitation of the hydrochloride gave a solid which was dissolved in N-methanolic potassium hydroxide and diluted with water. The base was extracted with ether. Drying and removal of solvent gave NN-*dimethylpregnan-3β-ylamine*, m. p. 124°, $[\alpha]_D$ +23° (*c*, 0·85) after recrystallisation from acetone [Found (after sublimation at 130°/0·01 mm.): C, 83·6; H, 12·2; N, 4·3. $C_{23}H_{41}N$ requires C, 83·3; H, 12·5; N, 4·2%].

(*b*) *Pregnan-3-one oxime* (350 mg.), m. p. 165—167°, $[\alpha]_D$ +66° (*c*, 0·97) [Found (material dried at 100°/0·02 mm. for 2 hr.): C, 79·8; H, 11·0. $C_{21}H_{33}ON$ requires C, 79·5; H, 11·1%], was reduced in ethereal solution with lithium aluminium hydride during 3 hr. Pregnan-3β-ylamine was isolated in the usual way as an oil, which, after distillation at 120—140°/0·02 mm., crystallised from ether in needles, m. p. 78° after softening from 65°; 3β-*acetamidopregnane*, prepared in the usual manner, crystallised from acetone in plates, m. p. 213° [Found (after sublimation at 230°/0·02 mm.): C, 79·6; H, 11·3. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·3%]. Methylation of the base with formaldehyde–formic acid gave *NN*-dimethylpregnan-3β-ylamine, m. p. 124° after sublimation at 140—150°/0·01 mm., and recrystallisation from acetone, identical with a specimen prepared by method (*a*).

NN-*Dimethylpregnan-3α-ylamine.*—Pregnan-3-one oxime (250 mg.) was treated with sodium in boiling ethanol. The product was isolated as an oil, which by sublimation at 120—140°/0·02 mm. gave crystalline material, m. p. 125—140° (polymorphic form ?); this by recrystallisation from ether gave pregnan-3α-ylamine as tiny prisms, m. p. 158—161°, $[\alpha]_D$ +43° (*c*, 1·0) [Found (after sublimation at 140°/0·02 mm.): C, 83·3; H, 12·0. $C_{21}H_{37}N$ requires C, 83·1; H, 12·3%]. 3α-*Acetamidopregnane*, prepared in the usual way, crystallised from acetone as plates, m. p. 220°, $[\alpha]_D$ +46° (*c*, 1·1) [Found (after sublimation at 200°/0·02 mm.): C, 79·4; H, 11·4. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·3%]. The base was methylated with formaldehyde–formic acid to yield an oil, which was obtained crystalline from acetone with some difficulty, and was chromatographed on a column of aluminium oxide. Elution by repeated washing with pentane gave an oil, which was sublimed at 110—130°/0·02 mm., and the sublimate crystallised with difficulty from acetone to yield *NN*-dimethylpregnan-3α-ylamine, m. p. 75—77°, after softening from 70°.

*Action of Dimethylamine on Pregnan-3β-yl Toluene-*p*-Sulphonate.*—The toluene-*p*-sulphonate (80 mg.) was treated at 110° with 33% (w/w) dimethylamine (2·5 c.c.) for 3 hr. The product was extracted with ether, washed with N-potassium hydroxide, and dried, and the solvent then removed. Chromatography of the product on aluminium oxide (2 g.), with pentane (15 c.c.) as eluant, gave an oil (5 mg.) whilst benzene (15 c.c.) furnished a solid (33 mg.) which after two crystallisations from acetone gave a base, $C_{23}H_{41}N$, m. p. 142—144° [Found (after sublimation at 140°/0·005 mm.): C, 83·1; H, 12·0%]. There was insufficient material to permit determination of $[\alpha]_D$.

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UNIVERSITY COLLEGE, SWANSEA, UNIVERSITY OF WALES. [*Received, October 8th*, 1954.]

The Polarographic Reduction of Tervalent Arsenic in Non-complex-forming Media.

By D. A. Everest and G. W. Finch.

[Reprint Order No. 5777.]

The polarographic reduction of tervalent arsenic has been studied in 0·1N-solutions of hydrochloric, nitric, perchloric, and sulphuric acids. The waves obtained were not satisfactory for analytical application. When 0·001% of methylene-blue was added to the solutions in 0·1N-hydrochloric and sulphuric acids analytically satisfactory waves were obtained possessing reproducible diffusion current constants for arsenic concentrations down to 10^{-4}M (or less accurately down to 10^{-5}M). Gelatin was shown to be unsatisfactory as a maximum-suppressing agent owing to the marked reduction it caused in the height of the arsenic wave. The formation of arsine during the reduction has been demonstrated, and an interpretation of the various sections of the unsuppressed wave has also been advanced.

The reduction of tervalent arsenic in dilute solutions of non-complex-forming acids gives rise to waves of high complexity which are somewhat unsatisfactory in analytical application (Kacirkova, *Coll. Czech. Chem. Comm.*, 1929, **1**, 477; Kruykova, *Zavod. Lab.*, 1940, **9**, 950; Bambach, *Ind. Eng. Chem. Anal.*, 1942, **14**, 265; Lingane, *ibid.*, 1943, **15**, 583). In general, the reduction of tervalent arsenic in the presence of complex-forming organic acids such as tartaric (Haight, *Analyt. Chem.*, 1954, **26**, 593), or its anodic oxidation in

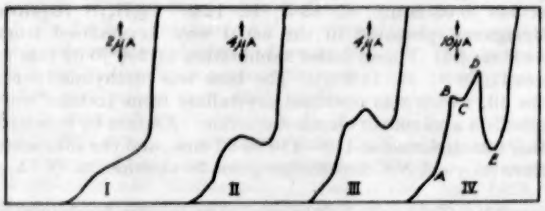


Fig. 1. *0·1N-Hydrochloric acid containing* (i) 0·05, (ii) 0·15, (iii) 0·20, *and* (iv) 0·60 × 10^{-3}M-*tervalent arsenic.*

alkaline media (Kolthoff and Probst, *ibid.*, 1949, **21**, 753; Cozzi and Vivarelli, *Analyt. Chim. Acta*, 1951, **5**, 215), has appeared to be of greater practical analytical utility. The present object has been to establish analytically satisfactory conditions for the reduction of tervalent arsenic in dilute solutions of non-complex forming acids, and also to obtain information concerning the various sections of the complicated polarograms obtained with a view to their possible interpretation.

Results and Discussion.—Experiments in absence of maxima-suppressors. Typical reduction waves of tervalent arsenic in 0·1N-hydrochloric acid are shown in Fig. 1, the effect of arsenic concentration on the heights of the various sections of these waves being shown in Fig. 2. Exactly equivalent behaviour was found in 0·1N-nitric, perchloric, and sulphuric acid. These waves, obtained in absence of suppressors, were not satisfactory for analytical application. As shown in Fig. 2, the heights of the points *A*, *B*, and *C* did not increase linearly with the arsenic concentration, the point *A*, indeed, reaching a constant current value above an arsenic concentration of *ca.* 2—3 × 10^{-3}M. The point *E*, whose current was approximately linear with the arsenic concentration, was too close to the peak *D* and the final hydrogen wave to allow of accurate measurement. That the reduction

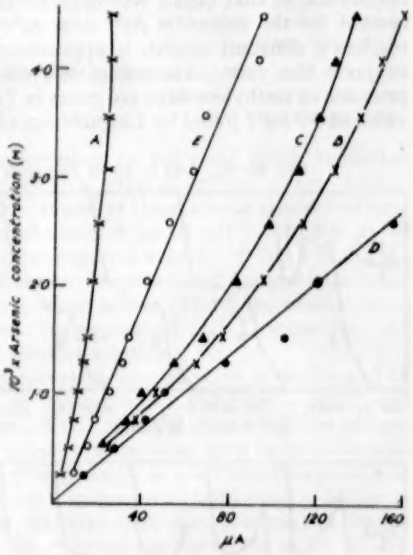
Table 1.

10^3[As] (M)	Potentials (v) vs. S.C.E.				10^3[As] (M)	Potentials (v) vs. S.C.E.			
	A	B	C	D		A	B	C	D
1·02	−0·70	−0·74	−0·92	−1·07	3·06	−0·73	−0·915	−1·02	−1·19
1·28	0·70	0·87	0·94	1·12	3·56	0·73	0·92	1·02	1·20
1·52	0·71	0·88	0·95	1·16	4·08	0·75	0·93	1·02	1·21
2·04	0·72	0·91	1·02	1·19					

was irreversible was indicated by the negative movement of the potentials of the various sections of the wave on increasing the arsenic concentration (Table 1), and also by the slope of the plot of E–log $i/(i_d - i)$ (0·11) for waves in the arsenic concentration range 1—2 $\times$ 10^{-4}M, *i.e.*, at arsenic concentrations at which relatively simple waves are obtained (Fig. 1).

Products of reduction. In agreement with Kacirkova (*loc. cit.*), we could detect visually the formation of elementary arsenic, starting from the foot of the reduction wave. However, as pointed out by Lingane (*loc. cit.*), the overall height of the arsenic wave is too great to be accounted for simply by a three-electron reduction to elementary arsenic, and it is necessary to postulate an overall six-electron reduction to arsine. That some arsine is formed on electrolysis of tervalent arsenic solutions at potentials 0·1 v more negative than that of the last section of the arsenic wave has already been demonstrated by Kruykova (*loc. cit.*); her work has now been extended, by use of a modified Gutzeit technique, to find exactly those sections of the arsenic wave associated with arsine formation. It was found that at potentials up to, and including, the point A no arsine could be detected, whilst at all potentials from the point B upwards arsine was found as a product of reduction. It appears, therefore, that up to the point A only elementary arsenic is formed and that A represents the limiting current for the reduction $As^{3+} \longrightarrow As^0$. Although it is well known that arsine, together with a large excess of hydrogen, is formed by electrolytic reduction of arsenic solutions at a mercury cathode (*e.g.*, Aumonier, *J. Soc. Chem. Ind.*, **1927**, **46**, 341), this is the first occasion on which such formation of arsine has been detected at potentials below that of hydrogen evolution.

FIG. 2. *Tervalent arsenic in* 0·1N-*hydrochloric acid.*



The fact that the point A reaches a constant height above an arsenic concentration of *ca.* 2—3 $\times$ 10^{-3}M is considered to result from the formation of a film of elementary arsenic on the surface of the mercury drop. This film interferes with the course of the electrode process, causing further reaction to occur at more negative potentials. Similar behaviour to this has been found in the polarographic reduction of quadrivalent selenium and tellurium (Lingane and Niedrach, *J. Amer. Chem. Soc.*, 1949, **71**, 196) and with bivalent germanium (Everest, *J.*, 1953, 660); in both cases analogous explanations to the above were advanced.

Turbulence effects. These were observed visually by addition of inert powders such as talc, charcoal, or graphite, the presence of which had no effect on the arsenic wave. From applied potentials of zero up to that of the point B only the normal motion of the liquid, due to the passage of the mercury drop, was observed. From B to the point D turbulence occurred, the motion of the liquid being directed upwards towards the drop, thus causing a swirling motion around the dropping electrode. At E the motion of the liquid was again normal. Identical behaviour was found in all four acids used. Attempts to view this turbulence in the presence of maxima-suppressors were unsuccessful since the added suppressors were simply adsorbed by the finely divided powders present.

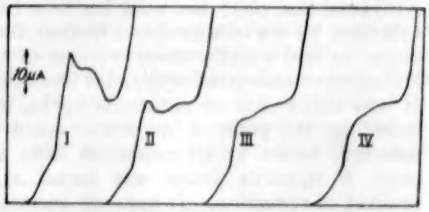
Effect of adding maxima-suppressors. Three suppressors have been tried, gelatin, methylene-blue, and sodium methyl-red, the effect of increasing concentrations of these substances on the arsenic wave being illustrated in Figs. 3*a*, 3*b*, and 3*c*. Of these substances gelatin was clearly unsatisfactory owing to the marked reduction it caused in

the overall wave height. In particular, with 0·003% of gelatin, the point *E* became too indistinct for its height to be measured at all. Methylene-blue was more satisfactory, addition of 0·001% eliminating the points *B*, *C*, and *D* whilst leaving the height of *E* entirely unaffected. Although addition of 0·001% of sodium methyl-red had little effect on the height of the point *E*, yet it did not completely eliminate either the point *B* or the subsequent dip in the diffusion current. The resulting waves were unsatisfactory for accurate analytical application as there was scarcely any horizontal section to the diffusion current before the onset of the hydrogen wave.

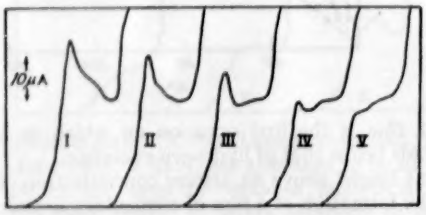
The constancy in the wave height of *E*, together with the lack of any abnormal turbulence at that point, was considered evidence that *E* represented the true diffusion current for the reduction $As^{3+} \longrightarrow As^{3-}$ ($n = 6$). The fact that the point *A*, before it reaches a constant height, is approximately half the corresponding value of *E* further supports this view. The values of *I* (the diffusion current constant) for the point *E* in presence of methylene-blue are given in Table 2; these values are to be compared with the value of 8·9 for *I* found by Lingane (*loc. cit.*) in 1·0N-hydrochloric acid in presence of 0·01%

FIG. 3*a*—*c*. 1·02 × 10^{-3}M-*Tervalent arsenic in* 0·1N-*hydrochloric acid containing:*

3*a* (i) 0·001%, (ii) 0·003%, (iii) 0·006%, *and* (iv) 0·009% *of gelatin.*



3*b* (i) 0·00005%, (ii) 0·0002%, (iii) 0·0006%, *and* (iv) 0·0010% *of methylene-blue.*



3*c* (i) 0·0001%, (ii) 0·0003%, (iii) 0·0005%, (iv) 0·0010%, *and* (v) 0·0015% *of sodium methyl-red.*

of gelatin; his lower value for *I* may be due to the higher acid concentration used, but it must also be partly due to the use of gelatin as maxima-suppressor.

That the points *B*, *C*, and *D* are simply maxima is indicated both by their ready elimination by maxima-suppressors and also by the abnormal turbulence observed at all three points. As *B* is the first point on the arsenic wave at which arsine can be detected it appears that *B* can be regarded as the normal maximum of the $As^0 \longrightarrow As^{3-}$ wave (*A*–*B*). That the point *D* is not a normal maximum like *B* is shown by the fact that it appears after the $As^0 \longrightarrow As^{3-}$ wave has apparently reached a limiting value (*C*). Although no explanation can be advanced concerning the true nature of the point *D*, its behaviour appears similar to that of the delayed maximum observed by Schwaer and Suchy (*Coll. Czech. Chem. Comm.*, 1932, **4**, 319) in the six-electron reduction of quadrivalent tellurium to hydrogen telluride in an ammoniacal medium. This maximum occurred after the tellurium wave had reached its limiting value, the wave returning to the limiting value after the maximum. The fact that with the arsenic wave the point *C* is higher than the point *E* is simply due to the closeness of the two peaks *B* and *D* which prevents *C* falling to the true diffusion current (*E*).

Unlike the behaviour in 0·1N-hydrochloric or sulphuric acid solutions of tervalent arsenic in 0·1N-nitric acid in presence of methylene-blue gave only poorly defined waves

which were useless for analytical application. Difficulty was also experienced in 0·1N-perchloric acid, where the addition of methylene-blue gave rise to a scarlet precipitate which caused erratic flowing from the mercury cathode.

TABLE 2.

t = 2·08 sec., m = 2·247 mg./sec., $m^{\frac{2}{3}}t^{\frac{1}{6}}$ = 1·938.

Arsenic trioxide in 0·1N-hydrochloric acid with 0·001% of methylene-blue.

10^3[As] (M)	Diff. current, μA	I	10^3[As] (M)	Diff. current, μA	I	10^3[As] (M)	Diff. current, μA	I
0·253	6·25	12·7	0·910	22·25	12·6	1·310	31·75	12·5
0·506	12·50	12·7	1·012	24·50	12·5	1·520	37·0	12·6
0·708	17·25	12·6	1·112	27·50	12·8	1·720	41·0	12·4
							Mean value	12·6

Arsenic trioxide in 0·1N-sulphuric acid with 0·001% of methylene-blue.

0·76	19·0	12·9	1·26	31·0	12·7	1·76	43·2	12·7
1·01	25·2	12·9	1·52	37·2	12·6		Mean value	12·8

Effect of pH. In order to determine the exact range of pH over which reduction occurred, 1×10^{-4}M-arsenic solutions were examined in a series of sodium acetate–hydrochloric acid buffers, a relatively simple wave being obtained at these arsenic concentrations. As the pH was increased, the wave height decreased (from 4 μA at pH 1·4 to 3·6 μA at pH 2·6) whilst the half-wave potentials shifted to more negative values (−0·765 v vs. S.C.E. at pH 1·4 to −0·905 v at pH 2·6). Beyond pH 2·6 accurate measurement became impossible owing to the interference with the hydrogen wave, whilst above pH 4·2 the arsenic wave became completely merged with that of hydrogen. In agreement with Lingane (*loc. cit.*) no reduction of tervalent arsenic was observed in alkaline solution.

Arsenic species present in solution. Since the tervalent arsenic wave is unchanged in shape, height, and position in 0·1N-solutions of hydrochloric, sulphuric, nitric, and perchloric acids (in absence of suppressors), it seems certain that the same reduction process occurs in all cases, and that the arsenic is largely present in the same form in all these acid solutions. This common form of the arsenic is probably As_2O_3 or a hydrated form such as H_3AsO_3. It has been observed by Kruykova (*loc. cit.*), and in an isolated case by Alimarin and Ivanov-Emin (*J. Appl. Chem. U.S.S.R.*, 1944, **12**, 204), that there is a marked change in the shape of the arsenic wave on increasing the chloride concentration to *ca.* 3—4M. This change is best explained by assuming that in chloride-rich media the arsenic is present largely as chloro-complex anions such as $AsCl_4^-$.

EXPERIMENTAL

A Tinsley polarograph incorporating a D.C. amplifier and a pen recorder was used throughout. Determinations were carried out in an H-type cell incorporating an external saturated potassium chloride calomel electrode (Lingane and Laitenen, *Ind. Eng. Chem. Anal.*, 1939, **11**, 504) which was immersed in a thermostat at 25° ± 0·15°. The resistance of this cell was less than 1000 ohms. Dissolved air was removed by passage of nitrogen. Solutions were made by dissolving 1 g. of arsenic trioxide in 500 ml. of water and dilution as required, no solutions more than ten days old being used in order to avoid ageing effects. The drop-times of the capillaries were determined at −1·25 v against S.C.E. in 0·1N-hydrochloric acid, and the mass of mercury flowing per second was measured in air on open circuit.

Detection of arsine. The apparatus used consisted of a glass 30-ml. cell incorporating a mercury-pool anode and a dropping-mercury cathode. A $4{\cdot}08 \times 10^{-3}$M-tervalent arsenic solution in 0·1N-hydrochloric acid (15 ml.) was first degassed with a stream of nitrogen and then electrolysed at the required potential for 2—3 hr. Electrolysis was then stopped and a stream of nitrogen passed through the solution to sweep out any arsine that had been formed. This nitrogen stream was then passed over mercuric chloride paper in a Gutzeit apparatus to detect the presence of arsine. Blank experiments showed that no stains were produced on the mercuric chloride paper by the simple passage of nitrogen through such solutions.

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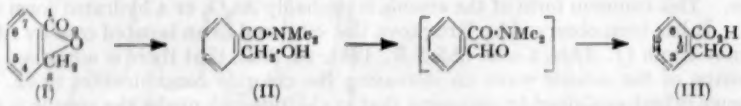
Lactones. Part I. A Novel Method for the Conversion of Phthalides into Phthalaldehydic Acids.

By JOHN BLAIR, J. J. BROWN, and G. T. NEWBOLD.

[Reprint Order No. 5813.]

Treatment of phthalides with dimethylamine gave the corresponding *o*-hydroxymethyl-*NN*-dimethylbenzamides, oxidation of which with chromium trioxide followed by hydrolysis with dilute hydrochloric acid furnished the phthalaldehydic acids.

THE experiments described in this Paper were carried out in an endeavour to find an efficient method employing mild conditions for the conversion of a phthalide (as I) into the corresponding phthalaldehydic acid (as III). The use of manganese dioxide in dilute sulphuric acid, *e.g.*, for the oxidation of meconin (6 : 7-dimethoxyphthalide) to opianic acid (5 : 6-dimethoxyphthalaldehydic acid) (Edwards, Perkin, and Stoyle, *J.*, 1925, **127**, 195), in our hands led to inconsistent results; it is dependent on the quality of the reagent and is difficult to stop at the required stage, with attendant formation of hemipinic acid. The use of lead dioxide in sulphuric or acetic acids or chromium trioxide in acetic anhydride appears unsatisfactory, *e.g.*, in attempts to oxidise 5 : 6-methylenedioxyphthalide to 4 : 5-methylenedioxyphthalaldehydic acid (Stevens and Robertson, *J.*, 1927, 2790). A useful method was developed (Hirshberg, Lavie, and Bergmann, *J.*, 1951, 1030; Brown and Newbold, *J.*, 1952, 4397) in which the phthalide was brominated by *N*-bromosuccinimide and the product hydrolysed to the phthalaldehydic acid; by use of this technique, phthalaldehydic acid, *m*-opianic (4 : 5-dimethoxyphthalaldehydic acid), and 4 : 5-methylenedioxyphthalaldehydic acid were efficiently prepared. This method may be more difficult to apply when an easily substituted nuclear position is present, *e.g.*, in meconin, though this oxidation has been accomplished (Blair and Newbold, forthcoming publication).



(I) (II) (III)

The oxidation of a ring-opened phthalide bearing a free hydroxymethyl group was desired; while such derivatives are formed in strongly alkaline solution the use of such a medium was undesirable in view of the Cannizzaro reaction of phthalaldehydic acids; *e.g.*, opianic acid gives meconin and hemipinic (3 : 4-dimethoxyphthalic) acid (Beckett and Wright, *J.*, 1876, **29**, 281). A feasible route seemed to effect the ring opening by the action of a secondary amine and to oxidise and then hydrolyse the amide under acid conditions. Though the ring opening of phthalides with hydrazine to give the *o*-hydroxymethylcarboxyhydrazide has been studied by Teppema (*Rec. Trav. chim.*, 1923, **42**, 30) little attention has been shown to the reaction of phthalide with ammonia or primary and secondary amines. While phthalide is reported to yield ammonium 2-hydroxymethylbenzoate when kept in aqueous ammonia (Hessert, *Ber.*, 1877, **10**, 1445), heating the lactone in an ammonia stream gave phthalimidine (Graebe, *Annalen*, 1888, **247**, 288). Theilacker and Kalenda recently (*ibid.*, 1953, **584**, 87) showed that phthalide gave 2-hydroxymethyl-*N*-methylbenzamide with aqueous methylamine.

Treatment of meconin with ethanolic dimethylamine at room temperature gave 6-hydroxymethyl-2 : 3-dimethoxy-*NN*-dimethylbenzamide (as II). The dimethylamide was readily hydrolysed by hot dilute hydrochloric acid or sodium hydroxide to meconin; when heated alone the dimethylamide decomposed at *ca.* 170°, evolving dimethylamine and giving back meconin. When the dimethylamide was oxidised for a short time with chromium trioxide in acetic acid in the cold and the oxidation product, not isolated in the solid state, was then heated with dilute hydrochloric acid, opianic acid was formed in 41% overall yield from meconin; under identical oxidation conditions meconin was unaffected.

This sequence of reactions has been successfully used for the preparation of phthalaldehydic acid, *m*-opianic acid, and 3-methoxy-, 4 : 5 : 6-trimethoxy-, and 5-methoxy-4-methylphthalaldehydic acid from the corresponding phthalides without isolation of the dimethylamides. The reaction of the phthalide with dimethylamine was carried out in ethanol in the cold and was followed by the oxidation and hydrolysis; if the phthalide was recovered unchanged the initial dimethylamine treatment was carried out at an elevated temperature in an autoclave and the process repeated.

6-Methoxyphthalaldehydic acid has been reported as a degradation product of mellein (ochracin), a compound produced by *Aspergillus melleus* Yukawa and *Aspergillus ochraceus* (Yabuta and Sumiki, *J. Agric. Chem. Soc. Japan*, 1934, **10**, 703). It has been synthesised by treatment of 7-methoxyphthalide with dimethylamine, to give 6-hydroxymethyl-2-methoxy-*NN*-dimethylbenzamide, followed by oxidation and hydrolysis. A convenient route to 7-methoxyphthalide has been developed starting from 3-methoxy-2-nitrobenzoic acid (Ewins, *J.*, 1912, **101**, 544) which was reduced to 2-amino-3-methoxybenzoic acid with sodium dithionite, the amino-acid being transformed by a Sandmeyer reaction into the nitrile which was then hydrolysed to 3-methoxyphthalic acid. 3-Methoxyphthalic anhydride was then converted into 7-methoxyphthalide by a modification of the procedure of Duncanson, Grove, and Zealley (*J.*, 1953, 1331). An unambiguous synthesis of 7-methoxyphthalide, albeit in small yield, has been achieved from 2-amino-3-methoxybenzoic acid by the reactions used by Brown and Newbold (*J.*, 1953, 1285) for the synthesis of 7-methoxy-6-methylphthalide.

The action of ethanolic ammonia in the cold on phthalide and meconin has been examined; *o*-hydroxymethylbenzamide and 2 : 3-dimethoxy-6-hydroxymethylbenzamide were formed respectively in good yield. It is interesting that on oxidation with chromium trioxide by the standard procedure each amide gave the corresponding imide of the dicarboxylic acid.

Experimental

Ultra-violet spectra were determined in EtOH unless otherwise stated, with a Unicam S.P. 500 spectrophotometer. pK_a values (classical) were determined as described in *J.*, 1954, 3935.

Standard Chromium Trioxide Oxidation Procedure.—A solution of the amide derivative (1 part) or, if the amide was not isolated as a solid, that derived from the phthalide (1 part) in glacial acetic acid (20 parts) was stirred at room temperature and treated with a solution of chromic acid (1 part) in water (1 part) and glacial acetic acid (20 parts) added in one portion and stirred for a further 5 min. Water (100 parts) was then added and the mixture extracted with chloroform (3 × 50 parts), and the combined extracts were washed with water, 10% aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4).

6-*Hydroxymethyl*-2 : 3-*dimethoxy*-NN-*dimethylbenzamide.*—Dimethylamine (50 c.c.) was added to a solution of meconin (2 g.) in ethanol (120 c.c.), and the mixture kept at room temperature for 2 days. After removal of solvent under reduced pressure below 35° the residual yellow gum slowly solidified; crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the *dimethylamide* (2·2 g., 89%) as plates, m. p. 93—95° (Found: C, 60·2; H, 6·8. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2%). The compound gave a 20° depression on admixture with meconin. Light absorption: Max. at 2080 (ε 29,400) and 2800 (ε 2300) and inflexion at 2260 Å (ε 11,500). The *acetate*, prepared in good yield by the action of acetic anhydride–pyridine at room temperature overnight, separated from light petroleum (b. p. 40—60°) as prisms, m. p. 63—64° (Found: C, 60·2; H, 6·6. $C_{14}H_{19}O_6N$ requires C, 59·8; H, 6·8%). Light absorption: Max. at 2080 (ε 32,600) and 2800 (ε 2400), and inflexion at 2260 Å (ε 12,500). The amide began to decompose at 170° (bath-temp.); after ½ hr. at 170—180° the residue was cooled and crystallised from ethanol, to give meconin (85%) as needles, m. p. and mixed m. p. 101—102°. Hydrolysis of the dimethylamide was slow in boiling water; boiling with 3N-hydrochloric acid for ½ hr. gave an almost quantitative yield of meconin. Boiling with 3N-sodium hydroxide also gave meconin in good yield.

Opianic Acid.—6-Hydroxymethyl-2 : 3-dimethoxy-*NN*-dimethylbenzamide (1 g.) was oxidised according to the standard procedure and the product isolated by using chloroform. Removal of the chloroform under reduced pressure gave a gum (700 mg.) which was refluxed with hydrochloric acid (10 c.c.; 3N) for 2 hr. On cooling, opianic acid (400 mg., 46%) separated;

it crystallised from water as needles, m. p. and mixed m. p. 145—146° (Found : C, 57·0; H, 5·0. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). Light absorption : Max. at 2150 (ε 20,700) and 2840 Å (ε 6500). Edwards, Perkin, and Stoyle (*loc. cit.*) give m. p. 146°.

Phthalaldehydic Acid.—Phthalide (2 g.) in ethanol (10 c.c.) was heated with dimethylamine (20 c.c.) in an autoclave at 130° for 4 hr. and then oxidised, and the product was hydrolysed as in the previous cases. Phthalaldehydic acid (20% yield) separated from benzene–light petroleum (b. p. 60—80°) as rosettes of needles, m. p. and mixed m. p. 97°.

m-*Opianic Acid.*—*m*-Meconin (500 mg.) and ethanolic dimethylamine (40 c.c.; 33%) were heated in an autoclave for 5 hr. at 140—145° and then oxidised and the product hydrolysed as in the previous cases. *m*-Opianic acid (40 mg.) was obtained from water as needles, m. p. 185—187° alone or mixed with an authentic specimen (m. p. 187—188°) (Brown and Newbold, *J.*, 1952, 4397).

3-*Methoxyphthalaldehydic Acid.*—4-Methoxyphthalide (0·5 g.) (Buehler, Powers, and Michels, *J. Amer. Chem. Soc.*, 1944, **66**, 417) was heated at 140—150° with ethanol (10 c.c.) and dimethylamine (35 c.c.) for 4 hr. The solution was evaporated under reduced pressure below 35° (bath-temp.), the residual gum oxidised according to the standard procedure, and the product hydrolysed to give 3-*methoxyphthalaldehydic acid* (210 mg.) crystallising from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 155—157°, pK_a 5·57 (Found : C, 59·9; H, 4·8%; equiv., 181. $C_9H_8O_4$ requires C, 60·0; H, 4·5%; equiv., 180). Light absorption in water : Max. at 2140 (ε 39,300), 2680 (ε 3100), and 3010 (ε 3900) and inflexion at 2350—2450 Å (ε 6800).

5-*Methoxy*-4-*methylphthalaldehydic Acid.*—6-Methoxy-5-methylphthalide (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, **23**, *B*, 17) (500 mg.) was heated with a 30% ethanolic solution of dimethylamine (70 c.c.) in an autoclave at 140° for 4 hr. The mixture was evaporated under reduced pressure below 40° to a gum, which was oxidised by the standard procedure, and the product was isolated by using chloroform. The chloroform extract was evaporated and the residual gum refluxed for 1 hr. with hydrochloric acid (20 c.c.; 3N), then cooled and the acid fraction isolated by way of chloroform. Crystallisation from benzene gave 5-*methoxy*-4-*methylphthalaldehydic acid* (200 mg.) as needles, m. p. 162—163° (Found : C, 62·1; H, 5·4%; equiv., 198. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%; equiv., 194). Light absorption in water : Max. at 2180 (ε 22,000) and 2900 (ε 9700) and inflexion at 2300—2340 Å (ε 12,900).

4 : 5 : 6-*Trimethoxyphthalaldehydic Acid.*—5 : 6 : 7-Trimethoxyphthalide (McRae, Van Order, Griffiths, and Habgood, *Canad. J. Chem.*, 1951, **29**, 482) (300 mg.) in ethanolic dimethylamine (50 c.c.; 33%) was heated in a sealed tube at 60° for 4 hr. and kept at room temperature for 2 days. The product, not isolated as a solid, was oxidised by the standard procedure, and the oxidation product hydrolysed to give 4 : 5 : 6-*trimethoxyphthalaldehydic acid* (50 mg.) which separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 137—138°, depressed on mixing with starting material (Found : C, 54·9; H, 5·3. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). Light absorption in water : Max. at 2230 (ε 20,500) and 2720 (ε 9600) and inflexion at 3120—3220 Å (ε 2800).

2-*Amino*-3-*methoxybenzoic Acid.*—Sodium dithionite (8 g.) was added in portions, with stirring, to 3-methoxy-2-nitrobenzoic acid (2 g.; Ewins, *J.*, 1912, **101**, 544) in a solution of potassium hydroxide (2 g.) in water (20 c.c.) at <40° (water-cooling). After ½ hr. at room temperature the solution was made acid (Congo-red) with hydrochloric acid (*d* 1·16) and heated on the steam-bath (fume-cupboard) for 3 hr. to remove sulphur dioxide. On cooling, 2-amino-3-methoxybenzoic acid (1·4 g.) separated. It had m. p. 164—166° (lit., m. p. 162—163°).

3-*Methoxyphthalic Acid.*—A suspension of 2-amino-3-methoxybenzoic acid (5 g.) in hydrochloric acid (7·5 c.c.; *d* 1·16) and water (25 c.c.) was diazotised at 0—5° with sodium nitrite (2 g.) in water (10 c.c.). After addition of urea the filtered diazonium solution was poured into a hot solution of potassium cyanide (8 g.) and copper sulphate (7 g.) in water (100 c.c.). The mixture was heated on the steam-bath for 1½ hr., cooled and acidified (Congo-red) with hydrochloric acid (*d* 1·16). The crude cyano-acid (4 g.) which separated was refluxed with aqueous potassium hydroxide (100 c.c.; 10%) for 4 hr. The solution was acidified (Congo-red) and evaporated to dryness under reduced pressure. The dark red residue was extracted with boiling ethyl acetate (3 × 100 c.c.); concentration of the extract to small bulk and cooling gave 3-methoxyphthalic acid (3·5 g.) as a brown solid, m. p. 162—165°. Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the acid as prisms, m. p. 169—171° (Bentley, Robinson, and Weizmann, *J.*, 1907, **91**, 104, give m. p. 173—174°) (Found : C, 54·9; H, 4·3. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%). Light absorption : Max. at 2110 (ε 22,500) and 3000 Å (ε 3400).

The crude acid (2 g.) was heated at 180—185° for 10 min. at atmospheric pressure and at

160—170°/10^{-3} mm.; 3-methoxyphthalic anhydride (1·8 g.) sublimed (m. p. 155—157°). Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave blades, m. p. 159—160° (Bentley *et al.*, *loc. cit.*, give m. p. 160—161°) (Found: C, 60·6; H, 3·5. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·4%).

7-*Hydroxyphthalide*.—3-Methoxyphthalic anhydride (4·4 g.), glacial acetic acid (13 c.c.), hydrochloric acid (13 c.c.; *d* 1·16), and zinc dust (11 g.) were heated under reflux for 6 hr. The mixture was kept at room temperature overnight and the filtered solution was almost neutralised with aqueous sodium carbonate, and extracted with chloroform (3 × 30 c.c.), and after being washed with water (20 c.c.) the dried (Na_2SO_4) extract was evaporated under reduced pressure to a gum (3·8 g.) which rapidly solidified. Separation of 4- and 7-methoxyphthalides by fractional crystallisation (cf. Duncanson, Grove, and Zealley, *loc. cit.*) proved impracticable. The solid was refluxed for 2½ hr. with aqueous hydrobromic acid (100 c.c.; *d* 1·46—1·49) in a coal-gas atmosphere. The solution was evaporated under reduced pressure to a red gum which was dissolved in water (50 c.c.) and treated with charcoal. The solution was evaporated to dryness under reduced pressure. The resulting solid (2·0 g.) was heated at 130—140°/10^{-3} mm., and the sublimate (1·4 g.), m. p. 125—127°, was collected. Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave 7-hydroxyphthalide as prisms, m. p. 134—136° (Found: C, 64·25; H, 4·3. Calc. for $C_8H_6O_3$: C, 64·0; H, 4·0%). Light absorption: Max. at 2120 (ε 26,000), 2320 (ε 8700), and 2990 Å (ε 4600). Eliel, Rivard, and Burgstahler (*J. Org. Chem.*, 1953, **18**, 1679) give m. p. 135—136·5°. The compound gave a purple colour with ferric chloride in aqueous ethanol.

7-*Methoxyphthalide*.—(*a*) 2-Amino-3-methoxybenzoic acid (5 g.) was refluxed for 3 hr. with lithium aluminium hydride (8 g.) in ether (250 c.c.). The mixture was worked up as given for the corresponding methyl derivative (Brown and Newbold, *J.*, 1953, 1285). Removal of the ether gave a light yellow, partially solid material (3·5 g.) which was used without further treatment for the next stage. A solution of the crude amino-alcohol in hydrochloric acid (27 c.c.; *d* 1·16) and water (90 c.c.) was diazotized at 0° with a solution of sodium nitrite (2·7 g.) in water (20 c.c.). After addition of urea the filtered solution was added to a hot solution of potassium cyanide (14·4 g.) and copper sulphate (12·6 g.) in water (150 c.c.). After being heated on the steam-bath for 30 min. the cooled mixture was extracted with ether (3 × 50 c.c.), and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated to a red oil (700 mg.). The oil was heated under reflux with aqueous potassium hydroxide (20 c.c.; 10%) for 2 hr. The solution was decanted from tar, acidified (Congo-red), and extracted with chloroform (3 × 20 c.c.), the combined chloroform extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Removal of the solvent gave an orange gum which slowly solidified. Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (charcoal) gave 7-methoxyphthalide (100 mg.) as needles, m. p. 107—109° (Found: C, 65·6; H, 5·1. Calc. for $C_9H_8O_3$: C, 65·85; H, 4·9%). Light absorption: Max. at 2090 (ε 33,000), 2340 (ε 8200), and 2960 Å (ε 4700). Duncanson, Grove, and Zealley (*loc. cit.*) give m. p. 96°; that this low m. p. was due to some residual 4-methoxyphthalide in the specimen has been shown by direct comparison of the infra-red spectra of the two substances. (We are indebted to Mr. J. F. Grove for this information.)

(*b*) 7-Hydroxyphthalide (650 mg.) was suspended in dry ether (5 c.c.) and treated with an ethereal solution of diazomethane (from 6 g. of nitrosomethylurea). Reaction and dissolution were rapid; after 6 hr. the solution was evaporated and the residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving 7-methoxyphthalide (570 mg.) as needles, m. p. 107—109° alone or mixed with preparation (*a*) (Found: C, 66·1; H, 5·1%). A specimen of 7-methoxyphthalide was demethylated under reflux with aqueous hydrobromic acid as given for the mixed phthalides, furnishing 7-hydroxyphthalide as prisms [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 132—134°.

6-*Hydroxymethyl*-2-*methoxy*-N*N*-*dimethylbenzamide*.—7-Methoxyphthalide (120 mg.) in ethanol (10 c.c.) was cooled to 0° and treated with dimethylamine (10 c.c.) and kept at room temperature for 3 days. Evaporation of the solution under reduced pressure below 35° and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave the *dimethylamide* (140 mg.) as blades, m. p. 120—121° (Found: C, 63·1; H, 6·8. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2%).

6-*Methoxyphthalaldehydic Acid*.—2-Hydroxy-6-hydroxymethyl-*NN*-dimethylbenzamide (100 mg.) was oxidised by the standard procedure and the product, isolated by chloroform, was refluxed for 1 hr. with hydrochloric acid (5 c.c.; 3N). 6-*Methoxyphthalaldehydic acid hydrate* (50 mg.), isolated by chloroform, crystallised from water as needles, m. p. 151—153° (Found: equiv., 198. $C_9H_8O_4,H_2O$ requires equiv., 198). After drying at 58°/0·5 mm. for 3 hr. the

anhydrous *form*, m. p. 151—153°, was obtained (Found : C, 59·7; H, 4·5%; equiv., 180·5. $C_9H_8O_4$ requires C, 60·0; H, 4·5%; equiv., 180). Light absorption in water : Max. at 2100 (ε 22,000), 2500 (ε 3900), and 3060 Å (ε 3200). The pK_a was 5·13. Yabuta and Sumiki (*loc. cit.*) give m. p. 152—153° for 6-methoxyphthalaldehydic acid obtained from degradation of mellein; a direct comparison of the two preparations has not been possible.

The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as yellow needles, m. p. 250—252° (decomp.) [lit., 245—246° (decomp.)] (Found : C, 50·3; H, 3·35; N, 15·8. $C_{15}H_{12}O_7N_4$ requires C, 50·0; H, 3·4; N, 15·55%).

o-*Hydroxymethylbenzamide*.—Liquid ammonia (200 c.c.) was added to a solution of phthalide (5 g.) in ethanol (100 c.c.) and kept overnight at room temperature, then evaporated under reduced pressure, and the residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give o-*hydroxymethylbenzamide* (75%) as blades, m. p. 149—150° (Found : C, 63·1; H, 5·9. $C_8H_9O_2N$ requires C, 63·6; H, 6·0%).

Phthalimide.—o-Hydroxymethylbenzamide (500 mg.) was oxidised according to the standard procedure. By means of chloroform, phthalimide (70% yield) was isolated and separated from water as needles, m. p. and mixed m. p. 235°.

6-*Hydroxymethyl*-2 : 3-*dimethoxybenzamide*.—Liquid ammonia (200 c.c.) was added slowly with shaking to a solution of meconin (5 g.) in ethanol (300 c.c.), and the solution kept overnight at room temperature. The solvent was removed under reduced pressure, to give a gum which slowly solidified. The solid was triturated with hot benzene, the benzene rejected, and the residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give 6-*hydroxymethyl*-2 : 3-*dimethoxybenzamide* (3·5 g.) as blades, m. p. 140—142° (Found : C, 57·0; H, 5·8. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2%). Light absorption : Max. at 2060 (ε 24,700) and 2820 (ε 2200) and inflexion at 2260 Å (ε 9300). The *acetate*, prepared in 80% yield by the action of acetic anhydride and pyridine at room temperature overnight and isolated by use of chloroform, separated from benzene–light petroleum (b. p. 60—80°) as blades, m. p. 159—160° (Found : C, 57·2; H, 6·1. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 6·0%). Light absorption : Max. at 2080 (ε 23,400) and 2820 (ε 2100) and inflexion at 2260 Å (ε 9250).

Hemipinimide.—Oxidation of 2 : 3-dimethoxy-6-hydroxymethylbenzamide (250 mg.) by the standard procedure, followed by isolation using chloroform and crystallisation of the product from ethanol, gave hemipinimide (100 mg.) as needles, m. p. 225—227° alone or mixed with a specimen prepared from opianic acid (Liebermann, *Ber.*, 1886, **19**, 2275; lit., m. p. 228—230°) (Found : C, 58·1; H, 4·4. Calc. for $C_{10}H_9O_4N$: C, 58·0; H, 4·4%). Light absorption : Max. at 2280 (ε 29,600) and 3320 (ε 5000) and inflexion at 2450 Å (ε 15,600).

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Some Reactions of cyclo*Propane and a Comparison with the Lower Olefins. Part I. Introduction, and Reaction with Strong Acids.*

By C. D. Lawrence and C. F. H. Tipper.

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The reaction of *cyclo*propane with moderately concentrated solutions of strong acids is about five times as fast as that of propene, but the kinetics are very similar for both gases. The rate is proportional to $[C_3H_6][acid]^n$, where n is large (6—10) with aqueous perchloric or sulphuric acids but lower (2·5—3·5) with sulphuric acid dissolved in acetic acid. The products of the absorption of *cyclo*propane in the three acid solutions have been investigated. A reaction mechanism is suggested, the first step being addition of a proton to the hydrocarbon.

It has long been known that the chemical properties of *cyclo*propane are more similar to those of the lower olefins, ethylene and propene, than to those of a higher member, such as *cyclo*pentane, of the *cyclo*paraffin series (see Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179, for discussion). Determinations of certain physical properties, *e.g.*, spectra and dipole moments, of *cyclo*propane derivatives have supported the view that the ring has some double-bond character (but see recent work by Eastman and Selover, *J. Amer. Chem. Soc.*, 1954, **76**, 4115, 4118), and Walsh (*loc. cit.*) has suggested that the carbon atoms in *cyclo*propane are in a state of trigonal hybridisation. However, the actual structure has been the subject of considerable controversy and so it was felt that further work on certain reactions of *cyclo*propane would yield results of interest.

The fact that both the lower olefins and *cyclo*propane are absorbed rapidly by concentrated solutions of strong acids to give esters has been known for a considerable time and is the basis of some methods for the analysis of these compounds. Davis and Schuler (*J. Amer. Chem. Soc.*, 1930, **52**, 721) and Rathmann (*J. Gen. Chem. U.S.S.R.*, 1937, **7**, 14) have investigated the rates of uptake by sulphuric acid solutions and the last showed that the absorption of *cyclo*propane was actually faster than that of propene, and that it was affected very markedly by the acid concentration. However, with the apparatus used, it is by no means certain that the results were not affected by the rate of physical solution of the gas in the acid, and no further deductions can be made. Hence, a more thorough study of the reactions of *cyclo*propane and propene with various acids was undertaken.

Experimental

The rate of reaction with various acids was followed by the conventional constant-pressure method. A certain volume of the acid was contained in a 50-ml. flask, immersed in a thermostat constant to $\pm 0{\cdot}1°$, and shaken about 250 times per min. The air in the flask had previously been swept out by *cyclo*propane or propene, and the rate of uptake of gas was followed by means of a gas-burette (in a thermostat) connected to the flask by wide capillary tubing and Polythene tubing. Before an experiment the flask was cleaned with concentrated nitric acid, water, alcohol, and redistilled water, and dried over a flame.

*cyclo*Propane was taken from a cylinder, passed through a solution of mercuric sulphate in 22% sulphuric acid, then water, and dried if necessary. Propene from a cylinder was washed and dried if necessary. "AnalaR" perchloric acid (72%), sulphuric acid, acetic acid, and methyl alcohol were used without further purification. Distilled water was redistilled in the presence of a little potassium permanganate in an all-glass apparatus. The potassium hydrogen sulphate and carbonate were of "AnalaR" standard.

Results.—The acids used were aqueous perchloric, aqueous sulphuric, and sulphuric in glacial acetic. Fig. 1 shows the results of two typical experiments. After a very rapid initial uptake due to physical solution of the gas, the rate of absorption (referred to hereinafter as the initial rate) remained constant for some time and then fell off. The initial rates were reproducible to about 5% with different specimens of the same concentration of any particular

acid, and were not affected by shaking speed provided this was above about 120 per min. It seems fairly certain therefore that the rate of uptake was equal to the rate of reaction.

The Table shows the effect on the initial rate of varying the pressure of the two gases. The results suggest that the order of the reaction with respect to *cyclo*propane or propene pressure is slightly greater than unity. However although it is unlikely that Boyle's law and Henry's law were accurately obeyed by either gas under the experimental conditions, it is probably true that the rate of reaction was approximately proportional to the concentration of *cyclo*propane or propene in the solution.

FIG. 1.

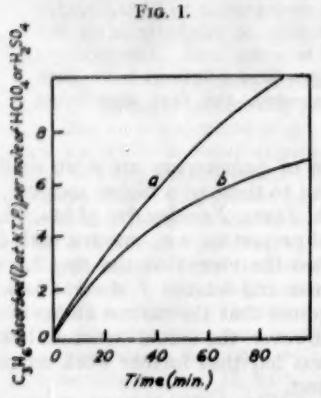

FIG. 2.

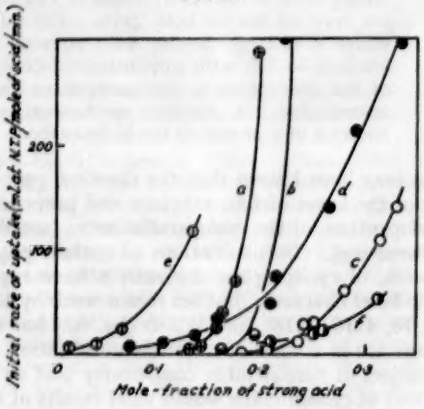

FIG. 1. *Typical* cyclo*propane uptake curves. Temp.* = 24·1°. C_3H_6 *pressure* = 760 *mm.*
(*a*) H_2SO_4 in AcOH, $N_{H_2SO_4} = 0{\cdot}260$.* (*b*) Aq. $HClO_4$, $N_{HClO_4} = 0{\cdot}203$ (abs. × 4).

FIG. 2. *Effect of acid concentration on the initial rate of uptake† of* cyclo*propane or propene, at* 24·1°/760 *mm.*

*cyclo*Propene and (*a*) aq. $HClO_4$ (ord. × 0·1), (*b*) $HClO_4$ in aq. MeOH (ord. × 0·1), (*c*) aq. H_2SO_4 (ord. × 0·5), or (*d*) H_2SO_4 in AcOH.
Propene and (*e*) aq. H_2SO_4 (ord. × 0·1; abs. × 0·2) or (*f*) H_2SO_4 in AcOH.

Variation of the rate of uptake of cyclo*propane or propene with the pressure of the gas.* Temp. = 24·1°.

Acid	Concn.* of added acid	Gas	Initial rate † P = 600	660	760	860	920	960
Aq. $HClO_4$	0·162	*cyclo*Propane	—	3·4	3·7	3·6	—	—
Aq. H_2SO_4	0·234	,,	—	6·5	6·5	6·8	—	—
,, ...	0·240	,,	13·3	—	14·2	—	—	14·8
,, ...	0·240	Propene	8·8	—	10·0	—	10·3	—
,, ...	0·265	,,	—	23·7	23·4	26·6	—	—
H_2SO_4 in HOAc	0·105	*cyclo*Propane	—	14·7	14·5	15·1	—	—

* N = Mole-fraction. † Ml. at P mm. and 0°, per mole of acid per min.

The variation of the rate of reaction with acid concentration is shown in Fig. 2. The curves have been modified to take into account, in an approximate fashion, the variation of physical solubility of the gases with variation of concentration of acid. With aqueous perchloric or sulphuric acid the initial rate increased very rapidly as the mole-fraction of the acid was increased, the apparent orders being roughly 6·3 and 7·5 for propene and *cyclo*propane respectively in aqueous sulphuric acid and 10 for *cyclo*propane in aqueous perchloric acid. With sulphuric dissolved in acetic acid, however, the increase in rate with increasing concentration of the former was more gradual, the apparent order with respect to H_2SO_4 being about 2·6 with *cyclo*propane and 3·5 with propene. The solubility of *cyclo*propane in acetic acid was about 14 times greater than in water. Replacement of part of the water in the perchloric acid by methyl alcohol (mole-fraction ~0·4) decreased the initial rate at any particular concentration of acid, although the solubility of the *cyclo*propane was 12—15 times greater in the presence of the alcohol. However, the order with respect to acid concentration

was still very high. Separate experiments showed that there was no appreciable reaction of methyl alcohol with aqueous perchloric acid under these conditions. There was no absorption of *cyclo*propane by glacial acetic acid alone or by concentrated aqueous potassium hydrogen sulphate. Addition of powdered silica (to increase the surface) had no effect on the rate of reaction of *cyclo*propane with aqueous perchloric acid within the experimental error.

The effect of temperature on the reaction rates is shown in Fig. 3. The overall activation energies calculated from the Arrhenius plots are 16·5 and 18·0 kcal./mole for the absorption in sulphuric in acetic acid of propene and *cyclo*propane respectively, and 13·8 kcal./mole for the absorption of *cyclo*propane in aqueous perchloric acid. Each of these values includes the appropriate heat of solution of the gas in the acid.

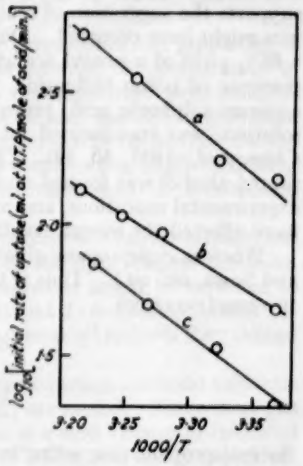

FIG. 3. *Effects of temperature on the initial rate of uptake of* cyclo*propane or propene at* 760 mm. *cyclo*Propane and (*a*) H_2SO_4 in AcOH ($N_{H_2SO_4}$ 0·260) or (*b*) aq. $HClO_4$ (N_{HClO_4} 0·203). (*c*) Propene and H_2SO_4 in AcOH ($N_{H_2SO_4}$ 0·249).

With aqueous perchloric acid, after relatively little uptake of *cyclo*propane an oily film formed on the walls of the reaction flask and when more gas was absorbed an oil separated which had a sharp smell and was almost certainly propyl perchlorate since its weight corresponded to the amount of gas taken up, within the experimental error. An oil also separated after relatively large absorption of *cyclo*propane in aqueous sulphuric acid. It was washed with a little water (the washings being added to the aqueous layer) and dried. Presumably it was di-*n*-propyl sulphate, which is only slightly soluble in water. However, although all the sulphuric acid was accounted for within the experimental error, either in the ester layer [the ester being assumed to be $(C_3H_7)_2SO_4$] or in the aqueous layer by titration with standard sodium hydroxide, about 30% of the gas taken up was not present in the form of propyl sulphate. Some propyl hydrogen sulphate was therefore probably formed. Absorption of *cyclo*propane in a solution of sulphuric in acetic acid did not lead to the formation of two layers. The whole was neutralised with solid potassium carbonate and extracted with ether, and the extract distilled. A fraction, b. p. 99°, with a smell of the lower esters of acetic acid was probably impure *n*-propyl acetate (b. p. 101·6°). The liquid residue left charred before distilling and probably contained di-*n*-propyl and/or propyl hydrogen sulphate.

The presence of the oily film, left on the surface of the flask until the next experiment, or of some of the non-soluble ester had no effect on the initial rates of uptake in the aqueous acids. The kinetics of the reaction were therefore not affected by the separation of the products.

DISCUSSION

The results show that the kinetics of the reaction between acids and both *cyclo*propane and propene are very similar, though the actual rates are, of course, different, and it is likely that the mechanism is the same in both cases. The lack of quantitative knowledge of the entities (molecules, ions, and ion-pairs) in solutions of strong acids of moderate concentration makes interpretation difficult, but the higher orders can probably be explained by analogy with third-order esterifications. Consider a simple scheme of three reactions:

$$(1)\ C_3H_6 + H^+ \longrightarrow C_3H_7^+$$
$$(2)\ C_3H_7^+ \longrightarrow C_3H_6 + H^+$$
$$(3)\ C_3H_7^+ + HX\ (\text{acid}) \longrightarrow C_3H_7X + H^+$$

If we assume that reaction (1) is slow, (2) very fast, and (3) moderately fast, the rate of uptake of gas $-d[C_3H_6]/dt = (k_1k_3/k_2)[C_3H_6][H^+][HX]$ to a first approximation. With aqueous perchloric or sulphuric acid, as the concentration of the solution was increased, the concentration of actual acid molecules would have increased rapidly from a negligible quantity in the dilute acids, and the reactions would exhibit a high apparent order. The decrease in rate of over 100-fold on replacement of a large part of the water in the aqueous

perchloric acid by methyl alcohol eliminates the possibility of any appreciable direct addition, $C_3H_6 + HX \longrightarrow C_3H_7X$, and could scarcely have been due to the decrease in dielectric constant. The protons were solvated, and it is reasonable to suppose that k_1 with H_3O^+ was very much greater than with $CH_3{\cdot}OH_2^+$. The formation of *n*-propyl acetate with sulphuric in acetic acid, together with the much lower order of reaction, supports the suggestion of reaction (3), although some addition of $C_3H_7^+$ ions to negative ions might have occurred. Dorris and Sowa (*J. Amer. Chem. Soc.*, 1938, **60**, 358) obtained a 65% yield of *n*-propyl acetate from the reaction of *cyclo*propane with acetic acid in the presence of boron trifluoride, probably by a similar mechanism. It is likely that, with aqueous sulphuric acid, propyl hydrogen sulphate was first formed, and, remaining in solution, was transformed into the dipropyl sulphate (cf. Plant and Sidgwick, *J. Soc. Chem. Ind.*, 1921, **40**, 14). Carbonium ions may be reactive towards water, but if any propyl alcohol was formed momentarily it would have reacted to give the ester under the experimental conditions, and an equilibrium $C_3H_7^+ + H_2O \rightleftharpoons C_3H_7{\cdot}OH + H^+$ would not have affected the overall result.

Whereas *cyclo*propane gives *n*-propyl esters, propene gives *iso*propyl esters (*e.g.*, Dorris and Sowa, *loc. cit.*). Thus if the first stage was the addition of a proton presumably the two reactions were

$$CH_3{\cdot}CH{=}CH_2 + H^+ \longrightarrow CH_3{\cdot}\overset{+}{C}H{-}CH_3$$

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!CH_2 + H^+ \longrightarrow \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!\overset{+}{C}H{-}CH_3$$

the *cyclo*propane ring acting in a similar way to the double bond. If this picture is correct then one reason why the rate of reaction of *cyclo*propane is greater than that of propene may be that the proton can attack any of three equivalent positions in the former but only one carbon atom in the latter.

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The Formation of iso*But-1-enyl Radicals from* iso*But-1-enylsilver. Part I.*

By F. Glockling.

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*iso*But-1-enyltriethyl-lead, $Et_3Pb{\cdot}CH{:}CMe_2$, with ethanolic silver nitrate at low temperature forms triethyl-lead nitrate and the orange, very unstable *iso*but-1-enylsilver. Evidence is presented that *iso*but-1-enylsilver decomposes into silver and *iso*but-1-enyl radicals $Me_2C{:}CH{\cdot}$, most of which dehydrogenate the solvent forming *iso*butene. Ethyl deuteroxide, $C_2H_5{\cdot}OD$, affords $Me_2C{:}CHD$. In the presence of excess of *iso*but-1-enyltriethyl-lead a chain reaction takes place whereby ethoxy-radicals attack the organo-lead compound giving further *iso*but-1-enyl radicals.

Detailed investigations of the decomposition of lead tetra-alkyls by silver nitrate, whereby free alkyl radicals are formed, have previously been confined to the saturated methyl, ethyl and *n*-propyl compounds. Semmerano, Riccoboni, and their co-workers (*Ber.*, 1941, **74**, 1089, 1297; *Z. physikal. Chem.*, 1941, **189**, 203; *Z. Elektrochem.*, 1941, **47**, 484) have shown that these lead alkyls react with alcoholic silver nitrate by an electron-transfer process, forming coloured unstable silver alkyls, RAg, and a trialkyl-lead nitrate:

$$R_4Pb + AgNO_3 = RAg + R_3PbNO_3$$

Methyl- and ethyl-silver, which are sparingly soluble in alcohol, decompose above −70° to silver and gaseous hydrocarbons. Ethane is formed exclusively from methylsilver, but ethane, ethylene, and *n*-butane from ethylsilver. These hydrocarbon products are consistent with decomposition of the intermediate alkylsilver into silver and alkyl radicals: $MeAg = Ag + Me\cdot$; $2Me\cdot = C_2H_6$. $EtAg = Ag + Et\cdot$; $2Et\cdot = n\text{-}C_4H_{10}$; $2Et\cdot = C_2H_4 + C_2H_6$. These reactions have been confirmed by quantitative kinetic studies (Bawn and Whitby, *Discuss. Faraday Soc.*, 1947, **1**, 228).

Since both the behaviour of unsaturated radicals and the preparation and properties of unsaturated organometallic compounds are of considerable interest, the preparation of *iso*but-1-enylsilver from *iso*but-1-enyltriethyl-lead and its decomposition were studied. *iso*But-1-enyltriethyl-lead, prepared from triethyl-lead chloride and *iso*but-1-enyl-lithium (Braude and Timmons, *J.*, 1950, 2007), is a colourless liquid, stable up to 140° in the absence of air, but slowly decomposed by air in daylight. Its constitution, $Et_3Pb\cdot CH{:}CMe_2$, was confirmed by its infra-red spectrum and by conversion by bromine to 1 : 1 : 2-tribromo-2-methylpropane and lead bromide.

Ethyl- or *iso*but-1-enyl-silver or both could result from reaction with silver nitrate, but the course of the reaction can be ascertained by analysis of the hydrocarbon products. *iso*But-1-enyl radicals from the decomposition of *iso*but-1-enylsilver might be expected to form *iso*butene (by extraction of hydrogen from the solvent) and 2 : 5-dimethylhexa-2 : 4-diene (by dimerisation of *iso*but-1-enyl radicals). In contrast to ethyl radicals they cannot react by simple disproportionation.

An orange precipitate, evidently *iso*but-1-enylsilver, is formed when alcoholic solutions of *iso*but-1-enyltriethyl-lead and silver nitrate (both at −78°) are mixed. There is no gas evolution. Gradual rise of temperature from −78° resulted in a slow change in colour of the precipitate from orange to pale blue-green, and above −20° silver was slowly deposited. The gaseous hydrocarbon produced contained 97—100% of *iso*butene (shown by combustion over copper oxide and bromine absorption). The composition of this gas was unchanged when the lead alkyl–silver nitrate ratio was varied from 1 : 1 to 140 : 1. It follows that silver nitrate removed exclusively the *iso*butenyl group under the conditions of the experiments. About 60—80% of the total *iso*butenyl present was recovered as *iso*butene; this shows that the *iso*but-1-enyl radicals, assumed to be intermediates, reacted mainly by abstraction of hydrogen from the solvent, *e.g.*, $CMe_2{:}CH\cdot + EtOH \longrightarrow Me_2C{:}CH_2 + EtO\cdot$.

Reactions carried out with excess of lead alkyl gave much more *iso*butene than corresponded with the amount of silver. This differs from the behaviour of tetramethyl-lead from which a mol. of ethane is formed for every two mols. of silver nitrate. Typical results obtained with *iso*butenyltriethyl-lead are shown in the Table. Much *iso*butene was formed

$AgNO_3$ used (mmoles)	$Et_3Pb\cdot CH{:}CMe_2$ (mmoles)	$Me_2C{:}CH_2$ (mmoles)	Pb/Ag	C_4H_8/Ag
1·24	1·24	0·795	1·0	0·64
0·473	0·678	0·412	1·43	0·87
0·237	0·678	0·522	2·86	2·21
0·118	0·623	0·534	5·28	4·52
0·237	1·36	1·12	5·74	4·68
0·0947	0·678	0·43	7·16	4·53
0·00473	0·678	0·181	143·3	38·2

with only catalytic quantities of silver nitrate, although the proportion of the total *iso*butenyl present recovered as *iso*butene was considerably reduced. These results indicate a chain reaction, and evidence for the following reaction sequence is discussed below:

$$Et_3Pb\cdot CH{:}CMe_2 + AgNO_3 \longrightarrow Et_3Pb\cdot NO_3 + Me_2C{:}CHAg \quad (1)$$

$$Me_2C{:}CHAg \longrightarrow Ag + Me_2C{:}CH\cdot \quad (2)$$

$$2Me_2C{:}CH\cdot \longrightarrow Me_2C{:}CH\cdot CH{:}CMe_2 \quad (3)$$

$$Me_2C{:}CH\cdot + EtOH \longrightarrow Me_2C{:}CH_2 + EtO\cdot \quad (4)\ *$$

$$Et_3Pb\cdot CH{:}CMe_2 + EtO\cdot \longrightarrow Et_3Pb\cdot OEt + Me_2C{:}CH\cdot \quad (5)\ *$$

$$2EtO\cdot \longrightarrow EtOH + CH_3\cdot CHO \quad (6)$$

* Chain propagation stages.

Reaction (1). Triethyl-lead nitrate (Löwig, *J. pr. Chem.*, 1853, **60**, 304) was with some difficulty isolated from the reaction in high yield. Previous workers have either assumed it to be formed or (Gilman and Woods, *J. Amer. Chem. Soc.*, 1943, **65**, 435) converted it into the readily isolated chloride. Conclusive analytical evidence that the orange precipitate initially formed was *iso*but-1-enylsilver was not obtained, but the presence of silver and the absence of lead and nitrate have been demonstrated by repeatedly centrifuging and washing the precipitate with ethanol at −78°: it afforded *iso*butene on decomposition in ethanol.

Reaction (2). Metallic silver was formed quantitatively in the overall reaction. In attempts to obtain direct evidence for the formation of *iso*butenyl radicals in solution, it was established that the yield of *iso*butene was hardly affected by the presence of oxygen or of 1 : 1-diphenyl-2-picrylhydrazyl. Failure to combine appreciably with the hydrazyl is remarkable since the activation energy for a radical–radical reaction should be less than for the hydrogen abstraction process (4).

Reaction (3). In the complete absence of ethanol or other solvent a high yield of 2 : 5-dimethylhexa-2 : 4-diene was obtained, and a silver mirror was deposited, in accord with the reaction sequence 1—3. In the presence of ethanol about 10% of the total *iso*butenyl was converted into the diene, which was estimated by its absorption at 242 mμ, and some diene was formed under all conditions investigated. The small amount of radical dimerisation observed in ethanol contrasts with the high yield of ethane obtained from tetramethyl-lead under similar conditions.

There was no evidence that *iso*butenyl radicals isomerise to the resonance-stabilised *iso*but-2-enyl radical, $\cdot CH_2 \cdot CMe{:}CH_2 \rightleftharpoons CH_2{:}CMe \cdot CH_2 \cdot$, and the absence of the dimer, $CH_2{:}CMe \cdot CH_2 \cdot CH_2 \cdot CMe{:}CH_2$, is evidence that such isomerisation did not occur.

Reaction (4). It is difficult to see how *iso*butene can be formed in this reaction other than by hydrogen abstraction by *iso*butenyl radicals. In the reactions carried out in solution, ethanol molecules are more numerous than any others and are the most likely source of hydrogen. On this reaction scheme the active product is either $C_2H_5 \cdot O \cdot$ or $CH_3 \cdot CH(OH) \cdot$. The relative ease of rupture of O–H and C–H bonds by *iso*butenyl radicals will depend on the bond energies and also on steric and polarisation factors. Phibbs and Derwent (*J. Chem. Phys.*, 1950, **18**, 495) have shown that high yields of ethylene glycol result from the mercury-photo-sensitised decomposition of methanol, indicating that the primary step is $CH_3 \cdot OH \longrightarrow \cdot CH_2 \cdot OH + H \cdot$. However, search for butane-2 : 3-diol by chemical and infra-red methods failed to reveal any. By adding a known quantity of this diol to the reaction mixture it was shown that if the reaction, $2CH_3 \cdot CH(OH) \cdot \longrightarrow [CH_3 \cdot CH(OH)]_2$, accounted for even 10% of the radicals formed from the alcohol the diol could have been detected by its infra-red spectrum after removal of alcohol and low-pressure distillation of the residue.

Evidence was obtained that at least a considerable proportion of *iso*butene was formed by abstraction of hydrogen from the hydroxy-group by using ethyl deuteroxide as solvent. The resulting [1-^{2}H]*iso*butene (possibly containing some *iso*butene) had a strong absorption band at 4·4 μ corresponding to the C–D stretching vibration. This contrasts with much other work involving attack by radicals on ethyl alcohol. For example, the peroxide- and light-induced addition of ethanol to olefins (Urry, Stacey, Huyser, and Juveland, *J. Amer. Chem. Soc.*, 1954, **76**, 450) was explicable only in terms of the formation of hydroxyethyl radicals: $Me_3C \cdot C \cdot + CH_3 \cdot CH_2 \cdot OH \longrightarrow Me_3C \cdot OH + CH_3 \cdot CH(OH) \cdot$. It is possible that [1-^{2}H]*iso*butene could have resulted from an exchange reaction between *iso*butene and solvent, ·EtOD, though this is considered rather unlikely in the slightly alkaline medium. Further work designed to clarify this point is in progress.

Reaction (5). A chain reaction involving the *iso*butenyltriethyl-lead must take place, to account for the high yields of *iso*butene relative to the amount of silver nitrate used, particularly at high lead alkyl–silver nitrate ratios. Reaction (5) seems the only feasible process though no triethyl-lead ethoxide was isolated (Leeper, Summers, and Gilman, *Chem. Reviews*, 1954, **54**, 143, report its m. p. as 18° but give no other details). In reactions involving an excess of lead alkyl a small quantity of white crystalline sublimate, identified as triethyl-lead hydroxide was always formed on removal of volatile materials at the

conclusion of a reaction. This could have resulted from the hydrolysis of the ethoxide by traces of water which might have been present, and, in fact, more triethyl-lead hydroxide was isolated when a little moist ethanol had been added to the residue from a reaction. This compound was never found in reactions between equimolar quantities of *iso*butenyltriethyl-lead and silver nitrate.

Reaction (6). Care was taken to use ethanol free from aldehyde and to exclude oxygen. After an experiment the solution gave a strong positive reaction for aldehydes. In addition to arising by reaction (6), acetaldehyde could result from the disproportionation of $CH_3 \cdot CH(OH) \cdot$ radicals.

As it was never possible to account for all the *iso*butenyl introduced in the form of the lead alkyl, it is likely that reactions other than those formulated above take place to a small extent, *e.g.*, the formation of a little *iso*butenyl ethyl ether, $Me_2C{:}CH \cdot + EtO \cdot \longrightarrow Me_2C{:}CH \cdot OEt$, and polymerisation involving *iso*butene and ethoxy- or *iso*butenyl radicals, $EtO \cdot + Me_2C{:}CH_2 \longrightarrow EtO \cdot CMe_2 \cdot CH_2 \cdot \longrightarrow$ etc. However it is difficult to account for the experimental observations on any basis other than the formation and subsequent reaction of *iso*butenyl radicals.

Experimental

The term N-c.c. refers to the volume a substance would occupy at N.T.P., *e.g.*, 1 mmole = 22·4 N-c.c. Analyses for lead were carried out by Saunders and Stacey's method (*J.*, **1949**, 919).

iso*But*-1-*enyltriethyl-lead.*—*iso*Butenyl bromide (27·0 g.) (Braude and Timmons, *loc. cit.*), which had been refluxed over sodium and fractionated (b. p. 91·5°/768 mm.), was added dropwise to refluxing ether (100 c.c.) and freshly cut lithium (3·0 g.) under nitrogen. Triethyl-lead chloride (19·0 g.) (Heap and Saunders, *loc. cit.*), suspended in dry ether, was then added and the mixture stirred and refluxed for 3 hr. Unchanged lithium was removed by filtration and the solution treated with ice-water. The ether layer was washed several times with water, dried ($MgSO_4$), and fractionated, and gave iso*but*-1-*enyltriethyl-lead* (15·7 g.), b. p. 99—101°/12 mm. (Found: C, 34·9; H, 6·6; Pb, 59·0. $C_{10}H_{22}Pb$ requires C, 34·35; H, 6·35; Pb, 59·3%). Its vapour pressure (mm.) is given by $\log_{10} p = 8{\cdot}65 - 2863/T$, whence the extrapolated b. p. is 224°. The mean latent heat (70—140°) 13·1 kcal./mole.

The presence of an *iso*butenyl group was confirmed by (*a*) the strong absorption band at 12·32 μ (Thompson and Torkington, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3) and (*b*) treatment with bromine in carbon tetrachloride, giving 1 : 1 : 2-tribromo-2-methylpropane, b. p. 83°/13 mm. (Found: C, 16·4; H, 2·5. Calc. for $C_4H_7Br_3$: C, 16·3; H, 2·4%).

Reactions between iso*Butenyltriethyl-lead and Silver Nitrate.*—(a) *In the absence of solvent.* An alcoholic solution of silver nitrate (0·476 mmole, 10·6 N-c.c.) was evaporated *in vacuo*, leaving silver nitrate finely dispersed over the surface of the vessel. A large excess of *iso*but-1-enyltriethyl-lead (~0·5 g.) was condensed on the silver nitrate and the mixture, which soon formed a silver mirror, was left at room temperature for 5 days. Fractional condensation of the volatile products in traps cooled to −20°, −65°, −78°, and −196° gave *iso*butene in the last (0·55 N-c.c.; completely absorbed by bromine in aqueous potassium bromide) and 2 : 5-dimethylhexa-2 : 4-diene (3·51 N-c.c.) from the trap at −65°. The diene formed transparent plates, m. p. 13·7°, b. p. (extrapolated) 133°, $\lambda_{max.}$ 2420 Å (Harper, Reed, and Thompson, *J., Sci. Food Agr.*, 1951, **2**, 94, record $\lambda_{max.}$ 2420 Å, ε 25,200).

(b) *In the presence of ethanol.* Stock solutions of silver nitrate and *iso*but-1-enyltriethyl-lead in ethanol (previously freed from acetaldehyde) were used. The former was kept in an amber, stoppered bottle, and the latter at 0°. In general, known volumes of each solution were introduced into two bulbs connected by a tube leading through an internally sealed joint about which part of the evacuated system could be rotated, and de-gassed by pumping at room temperature. The solutions were mixed at −78° and allowed to warm to ~ −30°; some of the ethanol was then back-distilled, thus allowing complete transfer of lead alkyl. Except where the concentration of silver nitrate was very low, an orange precipitate (considered to be *iso*but-1-enylsilver) was formed as soon as the two solutions were mixed at −78°. Above −50° the orange solid gradually became blue-green, while above −20° silver slowly separated from the solution both as a brownish-black sludge and as a mirror. Gas evolution became appreciable only above −10°.

Volatile products were separated after the mixture had been kept for 24 hr. at room temperature, and fractionally condensed with continuous pumping through two traps cooled to

−78° [to remove ethanol, $(Me_2C{:}CH)_2$, and any traces of lead compound], one trap cooled to −95° (to condense any acetaldehyde), and a liquid nitrogen trap (to condense *iso*butene). The condensation procedure was always repeated on the contents of the −78° traps. *iso*Butene was transferred by Töpler pump from a −95° bath to a gas burette and was characterised by combustion over cupric oxide at 500° and by bromine absorption. The combustion gave the amount of C_4 hydrocarbon in the range 97—100% and the latter 98—100% of unsaturated hydrocarbon.

Experiments illustrating the isolation of the various reaction products are as follows:

(i) Equimolar quantities (27·9 N-c.c.) of silver nitrate and *iso*but-1-enyltriethyl-lead were mixed at −78° (volume of solution, 36 c.c.), and *iso*butene (20·27 N-c.c., 72·7%) was isolated as described above. The non-volatile residue (containing $Et_3Pb{\cdot}NO_3$ and silver) was extracted with cold ethanol to remove triethyl-lead nitrate, and the silver in the residue estimated by standard methods, the recovery being 98·5%. Triethyl-lead nitrate was isolated by removing the ethanol *in vacuo* and pumping until a viscous oil was obtained. This was dissolved in *dry* benzene and filtered, and the benzene removed by rapid pumping without the application of heat, giving triethyl-lead nitrate (0·36 g.) as an intensely hygroscopic white power (Found: C, 20·1; H, 4·6; N, 4·1; Pb, 57·5. Calc. for $C_6H_{15}O_3NPb$: C, 20·2; H, 4·2; N, 3·97; Pb, 58·0%). Triethyl-lead nitrate is very soluble in most solvents except light petroleum. The contents of the −78° and −95° ampoules [ethanol, and traces of $(Me_2C{:}CH)_2$ and acetaldehyde] were removed from the vacuum-apparatus. The mixture gave positive qualitative tests for aldehydes, and negative tests for peroxides. Estimation of the 2 : 5-dimethylhexa-2 : 4-diene in a Unicam Spectrophotometer, $\varepsilon_{max.}$ being taken as 25,200 (cf. Harper *et al.*, *loc. cit.*), gave 1·2 N-c.c. of the diene.

(ii) *Reaction with excess of* iso*but*-1-*enyltriethyl-lead.* Ethanolic solutions containing silver nitrate (5·3 N-c.c.) and *iso*but-1-enyltriethyl-lead (30·4 N-c.c.) were mixed (total volume, 15 c.c.) *in vacuo* and treated as described, giving *iso*butene (25·04 N-c.c.; 82·4%). The residue accounted for 99·6% of the silver used. Estimation of 2 : 5-dimethylhexa-2 : 4-diene (2 N-c.c.) was only possible by first distilling the ethanolic solution from a bath at −20°. In addition to the diene peak at 242 mμ there was an unidentified stronger maximum at 249 mμ. When the volatile components were removed from the reaction vessel, a small amount of crystalline sublimate, triethyl-lead hydroxide, was formed on warming. This was sublimed on to a cold finger and purified by further sublimation in high vacuum at 60° (Found: C, 23·24; H, 5·1. Calc. for $C_6H_{16}OPb$: C, 23·1; H, 5·2%). Its aqueous solution was strongly alkaline. It partly melted at 50° and decomposed to a brown solid between 120° and 130° with gas evolution. Triethyl-lead hydroxide prepared by Saunders and Stacey's method (*J.*, 1949, 919) behaved similarly.

Reaction in the Presence of Deuteroethanol.—Deuteroethanol was prepared in a vacuum-apparatus from deuterium oxide and sodium ethoxide. Infra-red examination of the product showed a weak O–H band at 2·96 μ and a very strong O–D band at 4·2 μ. Silver nitrate (0·01 g.) was dissolved in the deuteroethanol (4 c.c.) and *iso*but-1-enyltriethyl-lead condensed on the mixture. After 2 days at room temperature the C_4 hydrocarbon was isolated in the usual manner (5·2 N-c.c.). The gas which is essentially [1-^{2}H]*iso*butene was completely adsorbed by bromine water; its infra-red spectrum showed a strong sharp peak at 4·4 μ corresponding to the C–D vibration.

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THE UNIVERSITY, LIVERPOOL. [*Received, November 1st*, 1954.]

The Hydrolysis of Titanium Tetraethoxide.

By D. C. Bradley, R. Gaze, and W. Wardlaw.

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The hydrolysis of dilute solutions of titanium tetraethoxide in ethyl alcohol has been studied. The products are complex and include a crystalline oxide ethoxide which has an unexpected composition. The oxide ethoxides of titanium undergo thermal disproportionation and also react in a complex manner with the Karl Fischer reagent.

Our knowledge of the esters of titanium is still far from complete. For a long time there was uncertainty whether the tetraethoxide was a liquid or a solid at room temperature. Demarçay (*Compt. rend.*, 1875, **80**, 51) described it as a white crystalline compound, but later, Bischoff and Adkins (*J. Amer. Chem. Soc.*, 1924, **46**, 256) concluded that when pure it was a liquid and that Demarçay's compound was an oxytitanate. Crowe and Caughlan recently (*ibid.*, 1950, **72**, 1694) reported that the distilled tetraethoxide solidifies and they suggested that it was a supercooled liquid at room temperatures. This conclusion has been confirmed by our experiments, which were carried out under rigorously anhydrous conditions. In case the change of state from liquid to solid should be associated with some degree of hydrolysis, we investigated the hydrolysis of titanium tetraethoxide in ethyl alcohol over a range of conditions, with interesting results. We find that dilute solutions of water in ethyl alcohol react instantly with the tetraethoxide and give a crystalline solid (I), so it appears that Demarçay's failure to prepare the tetrachloride as a pure liquid was due to his failure to exclude moisture, and that Bischoff and Adkins's view that his product was an oxytitanate is justified. The maximum yield of (I) was obtained when the molecular proportions of water to ethoxide were 1 to 2. However, substance (I) is not a simple derivative. Under varying conditions it gave analyses always within the limits Ti 25·7—26·1 and EtO 66·3—67·8%, even after many recrystallisations from specially dried ethyl alcohol, and molecular-weight determinations in benzene gave results of 832 by the ebullioscopic and 1040 by the cryoscopic method. Compounds which might compose substance (I) include :

Compound	Ti, %	EtO, %	Compound	Ti, %	EtO, %	Compound	Ti, %	EtO, %
(*a*) $Ti_2O(OEt)_6$	25·1	70·6	(*b*) $Ti(OEt)_3{\cdot}OH$	23·9	67·6	(*c*) $TiO(OEt)_2$	31·1	58·5

If (I) were a mixture of (*a*), (*b*), and (*c*), it would contain hydroxyl groups, but attempts to determine this group by reaction with either lithium aluminium hydride or ethylmagnesium iodide were unsuccessful, being complicated by side reactions.

It seemed probable that under the action of heat further condensation, $-Ti{\cdot}OH + -Ti{\cdot}OEt \rightarrow Ti{\cdot}O{\cdot}Ti + EtOH$, would take place. At 100° or higher (under reduced pressure) substance (I) disproportionated to give volatile tetraethoxide and a residue of titanium oxide diethoxide : a negligible amount of ethyl alcohol was formed either under these conditions or in solution in boiling benzene. Either the hydroxyl content of (I) is very low (*ca.* 0·1%) or the hydroxyl groups do not undergo condensation under the action of heat.

When equimolecular proportions of water and tetraethoxide in ethyl alcohol reacted, the resinous product gave an analysis close to that required by $TiO(OEt)_2$. The molecular complexity in benzene was 11·4. In further experiments the molecular proportion of water to ethoxide was progressively raised from 1·0 to 2·0. The titanium content and molecular complexity of the products rose steadily until the ratio reached *ca.* 1·75, whereat an insoluble white solid with an analysis close to that of diethoxydititanium trioxide $Ti_2O_3(OEt)_2$ was precipitated. Reactions involving higher proportions of water gave other insoluble products of a colloidal nature.

The oxide diethoxide was disproportionated at 200° under reduced pressure : titanium tetraethoxide distilled over, leaving a residue with an analysis near that of $Ti_2O_3(OEt)_2$. No further disproportionation occurred at this temperature and at 250° thermal decom-

position set in, so it appears that $Ti_2O_3(OEt)_2$ marks a change in the stability of the oxide ethoxides formed either by direct hydrolysis or by thermal disproportionation.

The possibility was considered that the crystalline titanium oxide ethoxide (I) might be a lattice compound of simpler units such as $Ti(OEt)_4$, $TiO(OEt)_2$, and $Ti_2O_3(OEt)_2$. On this basis it would be expected that the products of thermal disproportionation would recombine under suitable conditions. Accordingly, attempts were made to synthesise (I) by interaction of various proportions of titanium tetraethoxide with the resinous $TiO(OEt)_2$ in ethyl alcohol. Although small quantities of (I) were produced, the reaction was not quantitative.

In experiments to determine the hydroxyl content of (I) the reaction with the Karl Fischer reagent was studied. It was assumed that the hydroxyl group attached to titanium would react with the reagent in a manner analogous to that established by Gilman and Miller (*J. Amer. Chem. Soc.*, 1951, **72**, 2367) for the reaction involving hydroxyl bound to silicon as in $R_3Si{\cdot}OH$. The results indicated that (I) contained 6·75% of OH, a value inconsistent with the data obtained by other more direct methods. As titanium tetraethoxide does not react with the Karl Fischer reagent, it was concluded that (I) must contain a reactive group other than hydroxyl. When (I) was heated under conditions which caused no change in titanium content, its apparent hydroxyl content determined by the same reagent was now 2·0—2·6% instead of 6·75%, so the constituent being sought is eliminated by heating, and the reactions of the Karl Fischer reagent with the products of hydrolysis of the tetraethoxide were therefore examined.

In an experiment using the ebulliometer the elevation of the boiling point of ethyl alcohol was noted after the addition of some titanium tetraethoxide. Addition of water, sufficient to cause the formation of compound (I), gave an immediate decrease in the elevation; since this decrease must be associated with a change in complexity of the titanium compounds, the hydrolysis of titanium tetraethoxide must be instantaneous. However, it was surprising to find that a sample of the solution gave, with the Karl Fischer reagent, an apparent water content of some 90% of the amount originally added. Analyses of samples withdrawn at intervals during 5 hours showed a decreasing "apparent water content," although the elevation of boiling point remained constant.

In another experiment, in which the molecular proportion of water to tetraethoxide was 0·5 : 1, the solution was kept at the boiling point whilst samples were withdrawn for analysis after various times. The variation of "apparent water" content with time of heating is shown below:

Time, hr.	0	0·5	1·0	2·0	3·0	4·0	7·0	17·0
Apparent H_2O, %	85·8	82·9	81·2	63·4	52·0	46·3	35·1	36·6

Further experiments revealed that the apparent water content, determined immediately after the addition of water to the tetraethoxide, was dependent on the molecular proportions of reactants in the manner shown below:

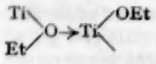
Mol. ratio H_2O : $Ti(OEt)_4$	0·5	1·05	1·69	2·67
Apparent H_2O, %	82	63	58	53

To summarise our results on the hydrolysis of titanium ethoxide we offer the following provisional interpretations. It is established that the reaction between water and titanium tetraethoxide in ethyl alcohol is very rapid and complete and that only a negligible percentage of hydroxyl groups remains in the products. It is also clear that an irreversible thermal disproportionation takes place, producing the tetraethoxide and more highly condensed compounds. Furthermore, it appears that disproportionation does not alter the number of osmotically active particles in solution because the average molecular complexity does not change. With regard to the reactions involving the Karl Fischer reagent we have found that titanium tetraethoxide is unaffected by this reagent whilst the compound (I) appears to contain water as do the other titanium oxide ethoxides to an extent which diminishes with increase in titanium content. Finally, a considerable proportion of the "apparent water" in (I) is eliminated by the action of heat either on the solid or in solution although the composition of (I) is otherwise unchanged.

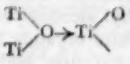
It is known that the Karl Fischer reagent does not react with acidic hydroxyl groups whereas it does so with basic ones. We suggest that bicovalent oxygen attached simply to titanium atoms, as in $\overset{\delta+}{\text{Ti}}—\overset{\delta-}{\text{O}}—\overset{\delta+}{\text{Ti}}$, may be sufficiently basic in the Lewis sense to react through the intervention of pyridinium ions, *e.g.*, :

$$(EtO)_3Ti{\cdot}O{\cdot}Ti(OEt)_3 + C_5H_5N^+ \longrightarrow (EtO)_3Ti{\cdot}OH + Ti(OEt)_3^+ + C_5H_5N$$
$$(EtO)_3Ti{\cdot}OH + C_5H_5N^+ \longrightarrow H_2O + Ti(OEt)_3^+ + C_5H_5N$$
$$2Ti(OEt)_3^+ + 2I^- \longrightarrow 2Ti(OEt)_3I$$

The oxygen linked as in Ti–OEt is not sufficiently basic to react because it is only combined with one titanium atom, the other link being to the more electronegative carbon. Moreover, it is known that in addition to titanium tetraethoxide's being trimeric, the titanium oxide ethoxides become increasingly complex as the proportion of ethoxide in the compound decreases. In the tetraethoxide it is probable that intermolecular bonding of the type



(II)



(III)

(II) is involved and in the highly condensed oxide ethoxides it seems probable that the bonding (III) occurs. The donor oxygen has a lower electron density than the simple Ti–O–Ti oxygen atom, and the former may be insufficiently basic to combine with the pyridinium ion and is thus unreactive. According to our interpretation, compound (I) is reactive because its high ethoxide content ensures that the complex molecules can utilise type (II) bonding rather than type (III), thus leaving a proportion of simple reactive Ti–O–Ti groups. However, in the more hydrolysed products, *e.g.*, $TiO(OEt)_2$, the Ti–O–Ti groups become deactivated with respect to combination with the pyridinium ion by being involved in type (III) bonding and thus the " apparent water " content decreases. The loss of reactivity with the Karl Fischer reagent caused by heating (I) is a logical consequence of the theory since the reactive compound (I) disproportionates to $Ti(OEt)_4$, which is inactive, and the higher oxide ethoxides [*e.g.*, $TiO(OEt)_2$], which are less active than (I). Accordingly, the data showing the relation between time and apparent H_2O content (above) must represent the rate of disproportionation of (I) in homogeneous solution. In quantitative terms it follows that if the hydroxyl and all of the oxygen exclusively bound to titanium in (I) react with the Karl Fisher reagent as outlined above, the " apparent hydroxyl " content would be 6·54% in satisfactory agreement with 6·5—7·1% found. In the case of $TiO(OEt)_2$, an " apparent water " content of 3·8% was determined by means of the Karl Fischer reagent. Thus it appears that in this compound, which has a maximum possible " apparent water " content of 11·7%, only about one-third of the oxygen exclusively attached to titanium is reactive to the Karl Fischer reagent This gives further support to our interpretation that the foregoing data represent the disproportionation of (I) into $TiO(OEt)_2$ and $Ti(OEt)_4$.

Experimental

As titanium ethoxide is extremely susceptible to hydrolysis, it was necessary in this work on controlled hydrolysis to take exceptional precautions to ensure that only predetermined quantities of water were involved in the reactions. In general, the methods adopted in recent work on the group IV alkoxides (*e.g.*, *J.*, 1954, 1091) were satisfactory. Water was excluded from the apparatus by phosphoric oxide guard-tubes. The ethyl alcohol was prepared from " absolute " alcohol by drying it first azeotropically with benzene, a 120-cm. fractionating column packed with Fenske helices being used, and then with sodium ethoxide and diethyl phthalate.

Analytical Methods.—Titanium and ethoxide were determined by methods already described (*J.*, 1952, 2773). Some of the ethoxide determinations were checked and confirmed by the Zeisel method.

Titanium Tetraethoxide.—Titanium tetrachloride (100 g.) was added dropwise with stirring

to an ice-cold mixture of ethyl alcohol (166 g.) and benzene (529 g.). Ammonia was then passed in until the exothermic reaction was complete. The ammonium chloride was collected on a sintered-glass (No. 3 porosity) Büchner funnel fitted with a loose cover through which a slow stream of dry nitrogen was passed to exclude atmospheric moisture. The residue was washed twice with benzene (100 c.c.), and the combined filtrate and washings were evaporated to dryness under reduced pressure. The viscous residue was distilled (b. p. 100°/0·1 mm.) and gave a mobile distillate (94 g.) [Found : Ti, 20·9; EtO, 78·7. Calc. for $Ti(OEt)_4$: Ti, 21·0; EtO, 79·0%]. A sample of the foregoing distillate was redistilled in an all-glass apparatus which had been dried finally by " flaming " at 0·05 mm. The distillate was sealed off under a vacuum and set aside. After a few days crystals were observed on the surface of the glass container, and after 2 weeks its contents appeared to be entirely solid. Warming melted the crystals at *ca.* 40°, and on cooling the liquid slowly re-solidified. After about 6 months the solid was re-melted and a sample analysed [Found : Ti, 20·9. Calc. for $Ti(OEt)_4$: Ti, 21·0%]. It is clear that titanium tetraethoxide can assume the solid state at room temperature and that the liquids reported by other workers were supercooled. Moreover, we were able to obtain crystalline titanium tetraethoxide from alcoholic solution. The freshly distilled tetraethoxide (10 g.) was dissolved in ethyl alcohol (30 c.c.), and the solution stored at *ca.* 20°. After 2 days a crop of finely divided white crystals had appeared. The crystals (1·8 g.) were separated, washed with alcohol by decantation, and dried at 0·1 mm. at room temperature [Found : Ti, 21·3%; *M*, ebullioscopic in benzene, 674. Calc. for $Ti(OEt)_4$: Ti, 21·0%; *M*, for trimer, 684]. These crystals had no sharp m. p. but softened slowly at *ca.* 100°.

Preparation of Compound (I).—The solution of water (0·65 g., 0·3 mol.) in ethyl alcohol (22 g.) was slowly added dropwise with magnetic stirring to the tetraethoxide (27·4 g., 1·0 mol.) in alcohol (56 g.). At the start of the addition the lower solution became turbid and a layer of finely divided white crystals was deposited. The mother-liquor was withdrawn with the aid of a sintered-glass immersion filter and the crystals were redissolved in warm alcohol (25 c.c.). The product which crystallised was separated as before, washed with alcohol, and dried at 0·1 mm. at room temperature (yield 9·5 g.) [Found : Ti, 26·1; EtO, 67·7%; EtO : Ti = 2·76; *M*, in benzene, 832 (ebullioscopic), 1040 (cryoscopic). " Apparent " water content, 6·75%]. The crystals softened between 90° and 100° and gave a clear liquid at 130°. Although sparingly soluble in cold alcohol, (I) was very soluble in other organic solvents and recrystallised with difficulty from benzene (Found : Ti, 26·4; EtO, 65·6%) or diethyl ether (Found : Ti, 25·7; EtO, 67·1%). The preparation of (I) was repeated several times with different initial proportions of water to tetraethoxide but, although the yield varied [maximum at 0·5 mol. of H_2O per mol. of $Ti(OEt)_4$], the composition was always within the range : Ti, 25·7—26·1; EtO, 66·3—67·8; " apparent " H_2O, 6·5—7·1%. For example, when water (2·44 g., 1 mol.) in alcohol (55 g.) was added to the tetraethoxide (30·9 g., 1 mol.) in alcohol (127 g.) no precipitate was observed until most of the alcohol had been removed by evaporation. After several days, the crystals (0·5 g.) were collected and dried as before (Found : Ti, 26·1; EtO, 66·3%).

Action of Heat on (I).—(*a*) A sample (0·447 g.) was heated at 110°/15 mm. for 8 hr. The crystals slowly melted to a cloudy viscous liquid. A trace of alcohol was detected in the cold trap and a loss in weight of 0·024 g. (5%) occurred. The " apparent " water content of the residue was 2·6%.

(*b*) The material (I) (2·68 g.) was heated at 200°/3 mm. for 2 hr. in an apparatus designed to collect volatile products which condensed at room temperature. The condensate (1·1 g.), a clear liquid, was titanium tetraethoxide (Found : Ti, 21·3; EtO, 77·2%). The residue was a highly condensed oxide ethoxide (Found : Ti, 35·7; EtO, 49·2%; EtO : Ti = 1·46).

(*c*) Substance (I) (2·0843 g.) was placed in the heating chamber of an all-glass apparatus which was fitted with a receiver cooled to *ca.* −80°. The apparatus was evacuated to 0·1 mm. pressure and isolated by a high-vacuum tap so that no volatile products could be lost during disproportionation. Heating at 90—100° for 1½ hr. caused the crystals to soften to a cloudy viscous liquid with a tendency to reflux. A trace of liquid which collected at *ca.* −80° was determined as ethyl alcohol (0·0061 g.) which agreed with the loss in weight of (I) (0·0054 g.). The residue (2·0789 g.) was dissolved in ethyl alcohol (3 c.c.), and the solution deposited crystals overnight. These (1·3 g.) were separated and washed with alcohol by decantation and dried in the usual manner and had the composition of (I) (Found : Ti, 26·0; EtO, 66·3%). However, the " apparent water " content had declined to 2·6% [cf. (I), 6·5%]. The ethyl alcohol produced in this experiment [0·3% of (I)] corresponded to only *ca.* 0·1% of OH in (I), the reaction being assumed to be $Ti{-}OH + Ti{-}OEt \rightarrow Ti{-}O{-}Ti + EtOH$. Since (I) may contain traces of alcohol as solvent, it appears that 0·1% is an upper limit for the hydroxyl content.

Next the action of heat on (I) in solution was studied: (*d*) Substance (I) (4·54 g.) was dissolved in ethyl alcohol (25 c.c.) at the b. p. and kept thereat for 3 hr. The solvent was then evaporated, and a highly viscous product (4·44 g.) obtained after prolonged drying at 95°/0·5 mm. (Found: Ti, 25·9; "apparent water," 1·95%).

(*e*) Benzene (50 c.c.) was refluxed in a fractionation apparatus (50-cm. column) and a small sample of distillate examined ($n_D^{22\cdot2}$ 1·4989); substance (I) (1·79 g.) was then added, and fractionation continued for 1 hr. No change in b. p. was observed, and examination of a small sample of distillate ($n_D^{22\cdot3}$ 1·4989) confirmed that no ethyl alcohol had been liberated. After removal of benzene, the residue (1·72 g.; Ti, 25·9%) which remained after drying at 95°/0·1 mm. had the same composition as (I).

Preparation of Titanium Oxide Diethoxide.—In the previously described experiment involving the addition of water (1 mol.) to titanium tetraethoxide (1 mol.) in ethyl alcohol the mother-liquor remaining after the removal of (I) (0·5 g.) was evaporated to dryness under reduced pressure. The viscous product slowly changed at 100°/0·1 mm. to a brittle resin [Found: Ti, 31·9; EtO, 55·6; "apparent water," 3·8%; *M*, in boiling benzene, 1730. $TiO(OEt)_2$ requires Ti, 31·1; EtO, 58·5%; *M*, 154]. This *oxide diethoxide* was highly soluble in organic solvents and crystallised with difficulty but unchanged in composition from ethyl alcohol (Found: Ti, 31·9; EtO, 56·2%) or light petroleum (Found: Ti, 31·5%).

Action of heat on the oxide diethoxide. This substance (1·6943 g.) was heated for 4 hr. at 200°/0·1 mm., and a colourless distillate (0·4292 g.) obtained [Found: Ti, 21·0. Calc. for $Ti(OEt)_4$: Ti, 21·0%]. The residue (1·2592 g.) was soluble in benzene (Found: Ti, 37·5%). The loss of 0·0059 g. of volatile products (0·35% based on oxide diethoxide) showed that only a trace of OH could have been present in the original compound. The foregoing residue (1·0043 g.) was heated for several hours at 250°/0·1 mm. and gave a mobile distillate (0·0931 g.) which smelled of impure ethyl alcohol. The final residue (0·8131 g.) was an inhomogeneous solid which was insoluble in benzene (Found: Ti, 44·6%).

Reaction of $TiO(OEt)_2$ *with* $Ti(OEt)_4$.—An attempt was made, by means of this reaction, to reverse the disproportionation of (I). The tetraethoxide (6·9 g.) and oxide diethoxide (1·9 g.) were refluxed in ethyl alcohol (18 g.) for 4 hr. A small amount of (I) (1·8 g. Calc.: 4·7 g.) (Found: Ti, 25·9%) was deposited on cooling. Other experiments were conducted with different proportions of the two reagents but only small quantities of (I) were produced.

Further hydrolysis of the oxide diethoxide. This substance (6·48 g.), dissolved in ethyl alcohol (57 g.), was treated with water (0·75 g.) in alcohol (30 g.) without noticeable effect. Warming caused precipitation of a voluminous solid, and the suspension was then boiled for 1 hr. The precipitate (3·5 g.) was separated, washed, and dried in the usual way (Found: Ti, 39·1; EtO, 40·4%. EtO : Ti = 1·10). The dry product was insoluble in organic solvents but the freshly precipitated solid, from a duplicate experiment, was soluble in benzene. Evaporation of this solution gave a resin which dried to an insoluble powder. Evidently the process of drying completes a stage in the polymerisation of this product.

Reactions involving the Karl Fischer Reagent.—(*a*) Water (0·048 g., 0·5 mol.) was added to the tetraethoxide (1·225 g., 1 mol.) in the absence of solvent, and the mixture stirred momentarily before addition of the reagent (10 c.c.) for the water analysis (Found: "water," 0·029 g., *i.e.*, 60% of initial amount).

(*b*) Aqueous alcohol (H_2O, 0·13 g., 1·0 mol.; EtOH, 3 g.) was added in the cold to a solution of the tetraethoxide (1·70 g., 1 mol.) in alcohol (18·67 g.). After warming to dissolve the crystalline precipitate, Karl Fischer reagent (45 c.c.) was added, and the "water" content determined (Found: "water," 0·116 g., *i.e.*, 89% of initial amount).

(*c*) Water (0·166 g., 1 mol.), tetraethoxide (2·105 g., 1 mol.), and alcohol (18 g.) were heated at the b. p. for 2 hr. before the cooled solution was analysed (Found: "water," 0·043 g., *i.e.*, 26% of initial amount).

(*d*) The effect of heat was further investigated. Water (0·41 g., 0·5 mol.) in alcohol (40·5 g.) was added to the tetraethoxide (10·45 g.) in alcohol (27·6 g.) and solvent was evaporated at room temperature until the residue weighed 31·5 g. The solution was then kept at the b. p. and samples were withdrawn periodically for determination of "water." The results, corrected for weights of samples withdrawn, are presented in the table on p. 722. It might appear from these results that the Karl Fischer reagent affords a means of following the rate of hydrolysis by determining the unchanged water. This was invalidated by the following experiment.

(*e*) The tetraethoxide (2·47 g., 1 mol.) was dissolved in alcohol (14·78 g.) in the ebulliometer, and the elevation of b. p. determined (0·315°). Water (0·0976 g., 0·5 mol.) added as 20%

aqueous alcohol caused an immediate fall in elevation (0·19°) and a sample withdrawn for analysis, showed a fall in water content (Found: "water," 0·089 g., *i.e.*, 91% of initial amount). Another sample withdrawn after 4 hr. showed a further decline in "water" content (Found: "water," 0·028 g., *i.e.*, 28·5% of initial amount) although the b. p. elevation was unchanged (0·20°, the slight increase was caused by removal of solution which effectively raises the solute concentration).

(*f*) The tetraethoxide (1·00 g., 1 mol.) was heated in boiling alcohol (12·2 g.), and water (0·039 g., 0·5 mol., as 20% aqueous alcohol) was added, and the solution immediately cooled and analysed for "water." Three more additions of water were made under similar conditions and the solution was analysed each time. The results, corrected for weights of ethoxide and alcohol removed at each stage, are presented in the table on p. 722.

Molecular Weights.—The cryoscopic measurements were conducted in an all-glass apparatus incorporating a Beckmann thermometer. Atmospheric moisture was excluded by a stream of dry nitrogen. The ebullioscopic measurements were made in the apparatus previously described (*J.*, 1952, 2027). The results are given below:

Compound	C_6H_6 taken, c.c.	Range of *m*, g.	$\Delta T/m$	*M*, found	Complexity, Ti atoms/mole
Cryst. $Ti(OEt)_4$	35·8	0·132—0·899	0·130°	674	3·0
(I)	35·6	0·393—2·037	0·106	832	4·5
$TiO(OEt)_2$	36·05	0·314—1·887	0·048	1730	11·4

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Normal Alkoxides of Quinquevalent Tantalum.

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Tantalum penta-alkoxides, $Ta(OR)_5$ where R = Me, Et, Pr^n, or Bu^n, have been prepared by the action of an alcohol and ammonia on tantalum pentachloride. Ebullioscopic measurements showed that the alkoxides were dimers in benzene, but in the parent alcohols the complexity depended on the alcohol. These data together with the boiling points under reduced pressure are discussed from the theoretical standpoint.

IN recent communications the results of a study of the tetra-alkoxides of group IVA elements have been recorded and the properties of these substances have been interpreted on a stereochemical basis. This involves the tendency of the central atom to increase its covalency by intermolecular bonding, which is opposed by the rotation of the alkoxide groups screening the central atom. To ascertain how widely this theory can be applied we have now studied the alkoxides of group V elements. We have confirmed that the reaction between tantalum pentachloride and alcohol yields hydrogen chloride and tantalum dichloride triethoxide $TaCl_2(OEt)_3$. The greater reactivity of tantalum pentachloride than of zirconium or hafnium tetrachloride is expected from the reactivity theory proposed by Bradley, Halim, and Wardlaw (*J.*, 1950, 3450). Thus the greater inductive effect of five than of four chlorine atoms attached to a central atom should cause an enhanced fractional positive charge on tantalum compared with zirconium and hafnium.

The literature contains no mention of the preparation and properties of tantalum penta-alkoxides. A range of normal penta-alkoxides of tantalum has now been prepared and examined. The following quantitative reactions take place:

$$TaCl_5 + 5NH_3 + 5ROH \longrightarrow Ta(OR)_5 + 5NH_4Cl \quad (R = Me, Et, Pr^n, \text{or } Bu^n)$$

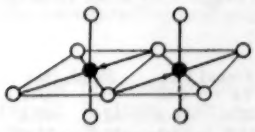
These alkoxides are colourless mobile liquids at room temperature [except $Ta(OMe)_5$, m. p. 50°]. They are extremely readily hydrolysed to tantalum pentoxide but can be

distilled under reduced pressure without decomposition. Their molecular weights have been determined ebullioscopically in benzene and in their parent alcohols (see Table 1).

TABLE 1.

R in $Ta(OR)_5$	B. p./10 mm.	M, in C_6H_6	M, in ROH	Mol. complexity in C_6H_6	Mol. complexity in ROH
CH_3	189°	664	404	1·98	1·20
C_2H_5	202	805	725	1·98	1·78
n-C_3H_7	232	927	809	1·95	1·70
n-C_4H_9	256	1102	763	2·02	1·40

Discussion.—The normal alkoxides of tantalum are dimeric in boiling benzene and show no change of complexity with concentration. This behaviour is readily explained on the assumption that tantalum attains a six-fold co-ordination with oxygen as shown inset. Moreover, it emphasises the contrast between quadrivalent and quinquevalent alkoxides in stereochemical requirements. For instance, in the case of zirconium alkoxides the lowest polymeric unit consistent with 6-co-ordinated zirconium is the trimer, higher polymers being possible, and experiments showed that the complexities of normal alkoxides of zirconium were between 3 and 4 (Bradley, Mehrotra, Swanwick, and Wardlaw, *J.*, 1953, 2025). The fifth alkoxide group present in tantalum alkoxides enables tantalum to realise the 6-co-ordinated state in the dimeric structure, which is the lowest possible polymer satisfying the stereochemical requirements. Further, the knowledge that tantalum normal alkoxides are dimeric in benzene solution enables us to rule out the possibility of tantalum's exhibiting a co-ordination number of 7 with oxygen in these compounds.



With regard to the molecular complexities of the alkoxides in their parent alcohols, two interesting points emerge. First, each alkoxide has a lower complexity in the alcohol than in benzene: this would be expected because the "donor" nature of the alcohols should favour monomeric alcoholates such as $Ta(OR)_5,ROH$ in solution; however, it is noteworthy that no alcoholates were isolated under our experimental conditions. Secondly, the variation of molecular complexity with the alcohol is suprising. Thus the order of molecular complexities is $Ta(OMe)_5 < Ta(OEt)_5 > Ta(OPr^n)_5 > Ta(OBu^n)_5$. The chief factors determining this behaviour are probably boiling point, dielectric constant of the alcohol, and electron-donating tendency of the alcoholic oxygen. It seems improbable that stereochemical factors are important because these alkoxides are all dimeric in benzene. The effect of boiling point on molecular complexity should be in the sense that raising the boiling point will lower the complexity owing to thermal dissociation of the dimeric molecules. On this basis alone, the molecular complexity should steadily diminish from methyl alcohol to *n*-butyl alcohol but this is not the case and it suggests that last two factors are also important. It is hoped that studies now in progress of the effects of temperature, dielectric constant, and donor power of the solvent on the molecular complexity of the alkoxide will throw further light on this interesting problem.

With regard to the boiling points of the tantalum penta-alkoxides it is noteworthy that the increment (13°) between the methoxide and the ethoxide is much less than the increments (30°, 24°) between the other alkoxides in ascending order of molecular weights. Thus it appears that the methoxide has an anomalously high boiling point, probably owing to greater intermolecular forces. More information on this point should be provided by forthcoming vapour-pressure measurements.

EXPERIMENTAL

The apparatus and experimental technique used were essentially similar to those previously described in our work on the group IVA alkoxides (*loc. cit.*). Owing to the ease with which tantalum alkoxides are hydrolysed, special precautions (*J.*, 1954, 1091) were taken to avoid hydrolysis.

The tantalum pentachloride was commercially available, niobium-free material and was used without further purification.

Determinations of tantalum were effected by precipitating hydrated tantalum pentoxide which was collected on a Whatman filter paper (No. 41) and ignited and weighed as Ta_2O_5. The determinations of methoxide and ethoxide were carried out by methods previously described (*loc. cit.*).

Reaction between Tantalum Pentachloride and Ethyl Alcohol.—Addition of ethyl alcohol (50 c.c.) to tantalum pentachloride (5 g.) caused a vigorous reaction with evolution of hydrogen chloride. The solution was evaporated to dryness under reduced pressure with final drying at 90°/0·5 mm. The finely crystalline solid (5·5 g.) [Found: Ta, 48·0; Cl, 18·0. Calc. for $TaCl_2(OEt)_3$: Ta, 46·8; Cl, 18·3%] gave a clear solution in water.

Preparation of Tantalum Alkoxides.—The method involved the addition of the appropriate alcohol to a suspension of the pentachloride in benzene, followed by treatment with excess of ammonia. The ammonium chloride was filtered off, and the filtrate evaporated under reduced pressure. In all cases the chloride-free tantalum alkoxide produced was distilled under reduced pressure, and the distillate was analysed. The details of these experiments are given in Table 2. The b. p.s were determined under a pressure of 10 mm. in an all-glass hypsometer, and the data are reported in Table 1.

TABLE 2.

R	ROH taken (c.c.)	$TaCl_5$ taken (g.)	C_6H_6 (c.c.)	$Ta(OR)_5$ Yield (g.)	B. p./0·2 mm.	Found (%) Ta	Found (%) OR	Reqd. (%) Ta	Reqd. (%) OR
Me	45·0	17·0	250	13·9 *	130°	53·8	46·2	53·8	46·1
Et	25·0	10·0	200	11·0	147	44·2	55·2	44·6	55·4
Pr^n	30·0	10·0	200	10·5	184	38·0	62·0	38·0	62·0
Bu^n	35·0	10·0	200	13·0	217	33·2	—	33·1	—

* M. p. 50° C.

TABLE 3.

Alkoxide	Range of m (g.)	Solvent (g.)	$\Delta T/m$	M Found	M Calc.
$Ta(OMe)_5$	0·052—0·813	15·59 [a]	0·285°	664	336
,, ...	0·069—0·365	16·35 [b]	0·236	404	,,
$Ta(OEt)_5$	0·182—0·432	14·65 [a]	0·250	805	406
,, ...	0·042—0·542	14·25 [a]	0·106	725	,,
$Ta(OPr^n)_5$	0·060—0·328	16·07 [a]	0·198	927	476
,, ...	0·055—0·415	15·74 [d]	0·126	809	,,
$Ta(OBu^n)_5$	0·075—0·290	15·93 [a]	0·168	1102	546
,, ...	0·033—0·128	16·93 [a]	(95·0 mm. [e])	763	,,

[a] Benzene; [b] methyl alcohol; [c] ethyl alcohol; [d] *n*-propyl alcohol; [e] *n*-butyl alcohol. [e] This boiling point elevation is in terms of mm. of water pressure difference in the water thermometer since no conversion tables are available for this temperature region.

Molecular Weights.—Molecular weights were determined in an all-glass ebulliometer incorporating a differential water-thermometer. The plot of $\Delta T°$ against weight of solute (m) was linear over the concentration range studied; the details are recorded in Table 3. An improved technique was devised to limit the error to $\pm 0·5\%$ and this will be described later.

We are indebted to Imperial Chemical Industries Limited for a Grant for the purchase of the tantalum pentachloride.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, October 9th*, 1954.]

The Structure of Acyl Nitrates.

By H. Burton and P. F. G. Praill.

[Reprint Order No. 5853.]

Acyl nitrates show little or no tendency to react in the form $R{\cdot}CO^+NO_3^-$. The possibility of a dual mode of ionisation is discussed.

In the search for other sources of acylium ions, it was decided to see if acyl nitrates ($R{\cdot}CO{\cdot}NO_2$) would give any evidence of acylium-ion formation. It is well known that acyl nitrates behave as nitrating agents, and that they readily undergo thermal decomposition (Lachowicz, *Ber.*, 1884, **17**, 1281; 1885, **18**, 2990; Francis, *J.*, 1906, **89**, 1) to the corresponding acid anhydrides:

$$2R{\cdot}CO{\cdot}NO_2 \rightleftharpoons (R{\cdot}CO)_2O + N_2O_5$$

The nitrating action of these compounds has been attributed (Gold, Hughes, and Ingold, *J.*, 1950, 2467) to a small but stationary concentration of dinitrogen pentoxide. The small amount of dinitrogen pentoxide could conceivably arise by the acyl nitrate dissociating slightly in the two possible ways:

$$R{\cdot}CO{\cdot}O{\cdot}NO_2 \rightleftharpoons R{\cdot}CO^+ + NO_3^-$$

and

$$R{\cdot}CO{\cdot}O{\cdot}NO_2 \rightleftharpoons R{\cdot}CO{\cdot}O^- + NO_2^+$$

the net result being:

$$2R{\cdot}CO{\cdot}O{\cdot}NO_2 \rightleftharpoons (R{\cdot}CO)_2O + N_2O_5$$

The previously reported unstable properties of benzoyl nitrate, prepared by Francis's method (*loc. cit.*) from powdered silver nitrate and benzoyl chloride at $-20°$, were confirmed. We have found, however, that the nitrate is more stable in solution, *e.g.*, in ether or methyl cyanide.

It was therefore decided to investigate a series of acyl nitrates prepared *in situ* from silver nitrate and acyl chloride, in an anhydrous solvent. The choice of solvent was largely governed by the low solubility of silver nitrate in most organic solvents and the desirability of using a solvent of high dielectric constant. Methyl cyanide ($\varepsilon \sim 39$) was finally selected. This method of preparation ensures that free hydrogen ion is not present (cf. Gold *et al.*, *loc. cit.*).

Solutions of benzoyl and *p*-methoxybenzoyl nitrate, kept at 0 to 5° for 2 hr., gave little indication of anhydride formation. 2 : 4 : 6-Trimethylbenzoyl nitrate gave small amounts of anhydride under these conditions, but the yields were not reproducible. Benzoic anhydride was not appreciably affected under the conditions used for the experiments.

It seemed that if these substances could exist in solution as acylium nitrates, $R{\cdot}CO^+NO_3^-$, then the addition of an acid to such a solution might produce more of the corresponding anhydride:

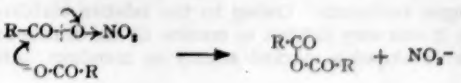
$$R{\cdot}CO^+NO_3^- + R{\cdot}CO_2H \rightleftharpoons (R{\cdot}CO)_2OH^+NO_3^- \rightleftharpoons (R{\cdot}CO)_2O + HNO_3$$

This would be more feasible than the alternative reaction:

$$R{\cdot}CO_2{-}NO_2^+ + R{\cdot}CO_2H \rightleftharpoons (R{\cdot}CO)_2O + HNO_3$$

since here, the acid would have to supply an acylium ion to produce the anhydride.

It is also possible that separation of the nitrate ion from the acyl nitrate is assisted by the attack of, *e.g.*, the 2 : 4 : 6-trimethylbenzoate anion:



The overall reaction would again lead to the anhydride and nitric acid. A similar mechanism might well operate for the attack of an acyl nitrate molecule on another provided that some separation into the ions NO_2^+ and $R{\cdot}CO{\cdot}O^-$ occurred. In this case the products would be the anhydride and dinitrogen pentoxide.

Addition of acid, equivalent to 0·5 mole per mole of acyl nitrate, to the nitrate solutions generally gave only inconclusive evidence of anhydride formation. However, in the case of 2 : 4 : 6-trimethylbenzoic acid and the corresponding nitrate, 2 : 4 : 6-trimethylbenzoic anhydride was obtained in 80% yield, based on the amount of acid added. Some nitrated 2 : 4 : 6-trimethylbenzoic acid was also obtained. In the light of these experiments it seemed that more conclusive results might be obtained from the systems: 2 : 4 : 6-trimethylbenzoic acid–benzoyl nitrate and 2 : 4 : 6-trimethylbenzoyl nitrate–benzoic acid. In both these cases only small amounts of non-crystallisable products, which may have been mixed anhydride, were obtained. Synthetic mixtures of benzoic and 2 : 4 : 6-trimethylbenzoic anhydrides readily re-solidified after fusion.

Concurrently with these experiments, another series was investigated in which anisole was added to the acyl nitrate solution. Clearly, if any of the acyl nitrate reacted as the acylium compound, $R{\cdot}CO^+NO_3^-$, some ketone should be produced:

$$PhOMe + R{\cdot}CO^+ \longrightarrow R{\cdot}CO{\cdot}C_6H_4{\cdot}OMe + H^+$$

The possible production of *p*-methoxyacetophenone by interaction of anisole with the methyl cyanide, *i.e.*, the Hoesch reaction, was also kept in mind, but was considered a less likely alternative, under the conditions employed. In none of the cases investigated, *i.e.*, acetyl, benzoyl, *p*-nitrobenzoyl, or 2 : 4 : 6-trimethylbenzoyl nitrate, was any ketone produced. Only in the last case was any anhydride obtained. Nitroanisole was the only product isolated in all these cases, and this was predominantly the *ortho*-compound, as was observed by earlier workers (Griffiths, Walkey, and Watson, *J.*, 1934, 631).

It is clear from these experiments that there is little evidence for the formation of free acylium ions from acyl nitrates. This is in accord with the fact that nitrogen has less affinity than oxygen for the electrons of the O–N bond. In the case of the acyl nitrates, the polarisation of the carbonyl group would tend to make the nitrogen more positive.

Most of the nitrates investigated were stable under the conditions employed but the formation of small amounts of 2 : 4 : 6-trimethylbenzoic anhydride shows that 2 : 4 : 6-trimethylbenzoyl nitrate is rather less stable. This compound is clearly favourably constituted for ionisation as an aroyl nitrate, $Me_3C_6H_2{\rightarrow}CO^+{\rightarrow}NO_3^-$, since here the combined electron-repelling effects of the three methyl groups would aid the separation of the nitrate ion. The effect of adding 2 : 4 : 6-trimethylbenzoic acid clearly indicates that ionisation, as distinct from dissociation, may be occurring in this way.

While the failure to isolate acid anhydride from most of the nitration experiments does not exclude the possibility that the nitration involves dinitrogen pentoxide, there is a good indication that the aroyl nitrate itself might be the nitrating agent under these conditions.

Experimental

Experiments without Anisole.—Acid chloride (0·05 mole), dissolved in an equal weight of methyl cyanide, was added during 15 min. to a cooled solution of silver nitrate (0·05 mole) in methyl cyanide (17·0 g.). The addition was carried out at 0—5° with constant shaking and then the mixture was left at 0—5° for 2 hr., with occasional shaking. There was no marked tendency for the temperature to rise, but the mixture invariably developed a pale yellow colour on being kept. The precipitated silver chloride was filtered off so that the filtrate dropped directly on to crushed ice. The silver halide (94—96%) was washed with ether and with water. After separation of the ethereal layer, the aqueous liquor was extracted twice more with ether. The combined ethereal extracts were washed repeatedly with water or with aqueous sodium hydrogen carbonate. Owing to the relative stability of the acyl nitrates under these conditions, it was very difficult to remove all the nitrate by this procedure. The ethereal extracts often developed a marked acidity on standing. After evaporation of the

dried (Na_2SO_4) ethereal solution, the residue was extracted with aqueous sodium hydrogen carbonate until free from acid and any residue was examined for anhydride.

In experiments where acid was also added, the appropriate compound (0·025 mole) was dissolved, together with the chloride, in a suitable quantity of methyl cyanide.

In most of these experiments the recovery of carboxylic acid was 88—94% of the theoretical amount.

2 : 4 : 6-*Trimethylbenzoyl Nitrate.*—This was prepared, as above, in the presence of 2 : 4 : 6-trimethylbenzoic acid (0·025 mole). The residue from the evaporation of the ethereal extracts was a waxy solid (6·4 g.) which crystallised readily from benzene–light petroleum as colourless flakes, m. p. 99—101°, which did not depress the m. p. of 2 : 4 : 6-trimethylbenzoic anhydride.

Acidification of the sodium hydrogen carbonate washings gave 6·0 g. of acid, which on extraction with light petroleum (b. p. 80—100°) gave some insoluble material (1·3 g.). The petroleum solution deposited crystalline material, m. p. 135°, that did not depress the m. p. of 2 : 4 : 6-trimethylbenzoic acid.

The sparingly soluble solid (later shown to be soluble to the extent of 1 part in 500 parts of boiling light petroleum, b. p. 80—100°) was recrystallised several times from light petroleum or benzene–light petroleum, and formed colourless prisms, m. p. 180°. A final crystallisation from aqueous ethyl alcohol gave material melting at 181° (Found : C, 57·7; H, 5·4; N, 6·6. Calc. for $C_{10}H_{11}O_4N$: C, 57·4; H, 5·3; N, 6·7%). Beringer and Sands (*J. Amer. Chem. Soc.*, 1953, **75**, 3319) give m. p. 180—182° for 2 : 4 : 6-trimethyl-3-nitrobenzoic acid.

2 : 4 : 6-*Trimethylbenzoic Anhydride.*—Dried sodium 2 : 4 : 6-trimethylbenzoate (4·5 g.) and 2 : 4 : 6-trimethylbenzoyl chloride (4·5 g.) in dry pyridine (35 ml.) were heated under reflux for 2 hr. The slightly impure anhydride (7·7 g.) was isolated by pouring the reaction mixture into ice-water. The brown solid crystallised from ethyl alcohol as colourless plates, m. p. 103—104° (Found : C, 77·0; H, 7·0. Calc. for $C_{20}H_{22}O_3$: C, 77·4; H, 7·0%). Fuson (*ibid.*, 1941, **63**, 2852) gives m. p. 106—107°.

Benzoyl Nitrate.—Freshly dried powdered silver nitrate (56 g.) in a flask fitted with a drying tube (P_2O_5), a dropping-funnel, and a thermometer, was shaken mechanically in an acetone–solid carbon dioxide bath. After being pre-cooled to −20°, benzoyl chloride (23 g.) was slowly added. Local overheating was unavoidable owing to the solidification of the benzoyl chloride and the general heterogeneous nature of the reaction mixture. The mixture was shaken at −17° to −13° for 2½ hr. Solid material was filtered off on a pre-cooled sintered filter and the filtrate was kept below −20°.

The nitrate was a pale yellow oil which hydrolysed readily with water. It decomposed on storage at room temperature with evolution of nitrogen dioxide; the residue gave some benzoic anhydride (m. p. and mixed m. p.).

Experiments with Anisole.—The anisole (0·1 mole) was added to the silver nitrate solution, prepared as above, before the addition of acid chloride. In these experiments there was often a marked tendency for the temperature to rise.

Results are collected in the following table.

R·COCl	Reaction time (min.)	Yield of nitroanisole (mole)
Acetyl	108	0·069
Acetyl + 0·2 mol. of Ac_2O	109	0·047
Benzoyl	135	0·064
p-Nitrobenzoyl	135	0·06
2 : 4 : 6-Trimethylbenzoyl	135	0·076

The fraction corresponding to nitroanisole in these experiments was collected at 128—132°/6 mm. (Found : N, 9·15. Calc. for $C_7H_7O_3N$: N, 9·15%).

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The Synthesis of Acyl Phosphates in Aqueous Solution.

By A. W. D. Avison.

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Reaction of phosphate anions with carboxylic acid anhydrides in aqueous media leads to biologically interesting acyl phosphates. The mechanism of the reaction, which is strongly catalysed by pyridine, is believed to involve two-point attack on the two carbonyl-carbon atoms of the anhydride. Diacetylmethylamine, azlactones, and acyl dialkyl phosphates can also act as acyl donors in the reaction. Convenient preparations are given for acetyl phosphate and other acyl phosphates. An analogous reaction takes place between tetramethyl pyrophosphate and salts of dibasic phosphoric acids.

Interest in acyl phosphates increased when Negelein and Brömel isolated 3-phosphatoglyceroyl phosphate as one of the intermediates of glycolysis (*Biochem. Z.*, 1939, **303**, 132) and as a result of the work of Lipmann and his colleagues and others on acetyl phosphate (see, *e.g.*, *Adv. Enzymology*, 1946, **6**, 231). Acetyl phosphate itself was first prepared by Lynen (*Ber.*, 1940, **73**, 367) by condensing silver dibenzyl phosphate with acetyl chloride, followed by hydrogenolysis of the benzyl groups from the product. This and other, more direct methods (Lipmann and Tuttle, *J. Biol. Chem.*, 1944, **153**, 571; Stadtman and Lipmann, *ibid.*, 1950, **72**, 1312; Bentley, *J. Amer. Chem. Soc.*, 1948, **70**, 2183; Koshland, *ibid.*, 1951, **73**, 4103), straightforward though they seem, involve, at some stage, the very unstable free acetylphosphoric acid.

In attempts to synthesise dinucleotide coenzymes by exchange reactions with acyl phosphates, it was discovered that the latter were produced with remarkable facility by the action of carboxylic anhydrides on phosphates in aqueous solution (B.P. Appln. 20,335/1953). This was originally modelled on the well-known Chattaway technique of acylation of phenoxide ions (*J.*, 1931, 2495) since the pK_3' of orthophosphoric acid is that of a very weak acid (*ca.* 11 as compared with pK' *ca.* 10 for phenol), although, as it later turned out, this would appear not to be an appropriate analogy. Trisodium phosphate was found to be readily acetylated by an excess of acetic anhydride at 0°, but the reaction proceeded best in the presence of sufficient sodium hydrogen carbonate to keep the pH between 7 and 8 throughout. By employing concentrated solutions and using the more soluble potassium salts, a useful preparative method for acetyl phosphate resulted. The method did not appear to possess any scaling-up difficulties, a neutral solution being maintained throughout, and gave yields of 40% of purified product. An almost identical procedure has since been described by Kaufman (*Arch. Biochem. Biophys.*, 1954, **50**, 506) for the preparation of succinyl phosphate.

Under such conditions, it was hoped that alcoholic hydroxyl groups present in sugar phosphates and nucleotides would not be esterified; in fact, α-D-glucose 1-phosphate, D-galactose 6-phosphate, D-riboflavin-5′ phosphate, and adenosine-5′ phosphate were even more readily attacked than orthophosphate ions by acetic anhydride in aqueous solution at pH 7—8, to give the corresponding acetyl phosphates. The same was found for aneurin mono- and di-phosphate, as well as inorganic pyrophosphate. Anhydrides other than acetic anhydride also acylate orthophosphate ions similarly, although with varying degrees of facility. In these reactions the hydrolyses both of reagents (very rapid) and of products (slower, but quite appreciable) prevent reliable estimation of relative rates. However, Table 1 gives the approximate conversions of orthophosphate into acyl phosphate under standard conditions: there is no obvious correlation with the strength of the parent acid, which would be some measure of the electrophilic properties of the carbonyl-carbon atom, and the high conversions of the cyclic anhydrides are striking. However, the cyclic anhydrides (maleic and succinic) had no measurable action on D-riboflavin-5′ phosphate or inorganic pyrophosphate under the same conditions.

A study of the effect of pH on the action of acetic anhydride on orthophosphate ions (Table 2) was rendered difficult by the need to choose buffers which would not be expected

to participate in the reaction. Consequently slight change of pH during the run was sometimes unavoidable, and the final pH in these cases is given in parentheses. The approximate distributions of the three ionic species were calculated from the published values of the apparent pK's of orthophosphoric acid (Kumler and Eiler, *J. Amer. Chem. Soc.*, 1943, **65**, 2355, for pK_1 and pK_2; Morton, *Quart. J. Pharm. Pharmacol.*, 1930, **3**, 438, for pK_3) which were unfortunately measured at temperatures and ionic strengths different from those employed in the present work. However, the figures serve as a rough guide, and

TABLE 1. *Acyl phosphates formed from carboxylic anhydrides* (10 *mols.*) *under standard* (*not optimal*) *conditions* (M-$NaHCO_3$ *at* 0°).

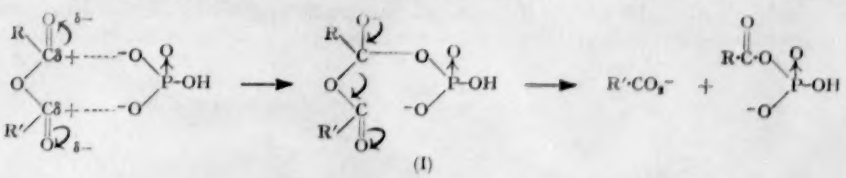
Anhydride	Conversion of HPO_4^{2-} (%)	10^3K_1 for parent acid	Anhydride	Conversion of HPO_4^{2-} (%)	10^3K_1 for parent acid
Benzoic	9	0·063	Phthalic	45	1·26
Chloroacetic	30	1·4	Succinic	60	0·066
Propionic	35	0·014	Maleic	85	15

TABLE 2. *Effect of* pH *on acetyl phosphate synthesis.*

Buffer	pH	Conversion (%) into acetyl phosphate in 30 mins.	Phosphate ions (%) initially present as: $H_2PO_4^-$	HPO_4^{2-}	PO_4^{3-}
M-Na_2CO_3	10·2 (9·7)	Nil	—	91	9
M-$NaHCO_3$ ..... / M-Na_2CO_3	9·15 (8·7)	Nil	—	99	1
M-$NaHCO_3$	7·95	22	7	93	—
M-NaOAc ..... / M-$NaHCO_3$ + AcOH ..... *	7·0 (6·85)	33	40	60	—
M-NaOAc ..... / M-$NaHCO_3$ + AcOH ..... *	6·1 (5·5)	20	83	17	—
M-NaOAc + AcOH	4·95 (4·75)	*ca.* 4	99	1	—
M-NaOAc + AcOH	4·05	Nil	100	—	—

* Prepared at 0° to minimise loss of CO_2.

show that the conversion falls drastically as the proportion of HPO_4^{2-} drops. The similar fall at higher pH's is due to the rapid increase in rate of hydrolysis of the acetic anhydride which, under these conditions, after 10 mins., was 95% complete at pH 8, 72% at pH 7, and only 60% at pH 6. Acetate ions had no measurable effect on the rate of orthophosphate liberation from lithium acetyl phosphate in M-sodium hydrogen carbonate, suggesting that the reverse change, $AcO^- + Ac{\cdot}PO_4^{2-} \longrightarrow Ac_2O + PO_4^{3-}$, does not occur to a significant extent. The observed conversions into acetyl phosphate therefore seem to be a function of the true rate of reaction at the starting concentration of acetic anhydride on which is superimposed the steadily changing effect of the hydrolysis of the latter. These facts suggest a mechanism for the reaction based on two-point attack of the doubly negatively charged phosphate anion on the two carbonyl-carbon atoms of the anhydride:

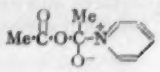
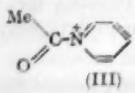


(I)

Such a mesomeric transition state would provide conditions for the necessary low activation energy of this ready reaction in a strongly hydrolytic medium.

When 2M-aqueous pyridine (pH 7·8) was used as buffering medium instead of sodium hydrogen carbonate, a remarkably rapid and almost quantitative conversion of orthophosphate into acetyl phosphate occurred in spite of the pronounced catalysis of the hydrolysis both of acetic anhydride (Bafna and Gold, *J.*, 1953, 1406) and of acetyl phosphate

(Koshland, *J. Amer. Chem. Soc.*, 1952, **74**, 2286) by pyridine. The increased rate of synthesis is unlikely to involve the 1-acetylpyridinium ion (III) (cf. Koshland, *loc. cit.*; Gold and Jefferson, *J.*, 1953, 1409) since in an overwhelmingly aqueous environment this highly reactive entity would almost certainly be attacked primarily by water. For the hydrolysis of acetic anhydride, Gold and Jefferson (*loc. cit.*) point out that the ion (II)

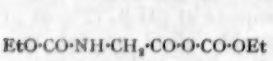
(II)   + AcO^-

(III)

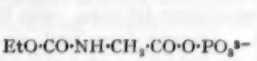
would approximate to the transition state in the rate-determining step of formation of (III) which then undergoes virtually instantaneous hydrolysis. Since the acetylation of phosphate ions has a reaction velocity at least comparable with that of the hydrolysis of acetic anhydride, and since the very large concentration of water will not be relevant for the catalysed hydrolysis until the ion (III) has been formed, the structure (II) might approximate to an activated acceptor of HPO_4^{2-} in the scheme outlined above. An alternative, but less likely, explanation would be that pyridine intervenes, not at the initial step, but in assisting the breakdown of (I) or some similar intermediate.

In further support of the proposed mechanism, acyl chlorides (*n*-butyryl and benzoyl) do not form measurable amounts of acyl phosphates in aqueous solution, and no evidence has been obtained of the reaction of acetic anhydride with dibenzyl phosphate, 2′ : 3′-*O*-*iso*propylidene adenosine-5′ benzyl phosphate, or betaine, which have only a single negatively charged oxygen atom.

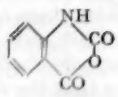
In preparative procedures pyridine is superior to sodium or potassium hydrogen carbonate owing to the higher and more rapid conversions, and also to the greater ease of separation of the products. Dilithium acetyl phosphate and sodium D-riboflavin-5′ acetyl and monochloroacetyl phosphate have been prepared in this way. Benzoic anhydride, which reacted only sluggishly with orthophosphate in the presence of sodium hydrogen carbonate, reacted almost quantitatively in the presence of pyridine. On the other hand, succinic anhydride was without effect on D-riboflavin-5′ phosphate in aqueous pyridine or aqueous sodium hydrogen carbonate, conceivably owing to steric interference with the formation of the transition state.



(IV)

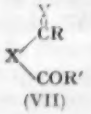


(V)

 (VI)

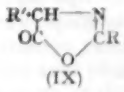
The mixed anhydride (IV) reacted readily with orthophosphate ions to give the corresponding glycyl phosphate derivative (V); but isatoic anhydride (VI) did not react. The more reactive *N*-carboxy-anhydrides of α-amino-acids might well be usable, however, as a source of free aminoacyl phosphates.

Some analogous compounds were also investigated. Diacetylmethylamine (VII; X = MeN, Y = O, R = R′ = Me) reacted sluggishly and incompletely with orthophosphate in aqueous pyridine, but not in aqueous sodium hydrogen carbonate.



(VII)

(VIII)



(IX)

Diacetylaniline (VII; X = PhN, Y = O, R = R′ = Me) on the other hand did not react to any measurable extent under either set of conditions. It is interesting that, since the completion of this work, Stadtman and White (*J. Amer. Chem. Soc.*, 1953, **75**, 2022) have briefly reported that *N*-acetylglyoxaline (VIII; R′ = Me) acetylates orthophosphate ions in aqueous solution at pH 7·0 in 50% yield: glyoxaline has a relatively high acid strength (pK ~7·0) and its *N*-acyl derivatives (VIII) are known to be reactive anhydride analogues

(Wieland and Schneider, *Annalen*, **1953**, **580**, 159), and probably acylate phosphate ions by a mechanism similar to that of the carboxylic anhydrides (VII; X = Y = O), all the structural features of the latter being present.

Azlactones (IX) are also related structurally, being cyclic iminoacyl analogues of (VII), and the compounds (IX; R = Ph, R′ = H; and R = Me, R′ = Ph·CH_2) reacted quantitatively with orthophosphate in aqueous pyridine to give benzoylglycyl phosphate (X) and *N*-acetylphenylalanyl phosphate (XI), respectively. In addition, the latter azlactone with adenosine-5′ phosphate gave 81% of the compound (XII).

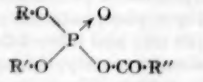
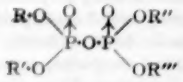
(X) $Ph{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}PO_3^{2-}$ $CH_3{\cdot}CO{\cdot}NH{\cdot}\underset{\displaystyle CH_2Ph}{\underset{|}{C}}H{\cdot}CO{\cdot}O{\cdot}PO_3^{2-}$ (XI)

Adenosine-5′-O·PO(O^-)·O·CO·CH(CH_2Ph)·NHAc
(XII)

The phosphates (X) and (XI) reacted readily with aniline in aqueous solution, but not with glycine at pH 8—9. Under the same conditions, the adenosine compound (XII) gave *N*-acetylphenylalanylglycine, identified by paper chromatography, confirming Chantrenne's contention (*Compt. rend. Lab. Carlsberg, Sér. Chim.*, 1948, **26**, 297; *Nature*, 1949, **164**, 576) that only acyl phosphates with one ionisable acid group react with amino-acids in aqueous solution.

*iso*Propenyl acetate (VII; X = O, Y = CH_2, R = R′ = Me), although an active acetylating agent under anhydrous, acid-catalysed conditions, did not react with aqueous orthophosphate ions, or appreciably with aqueous hydroxylamine at pH 6, and therefore cannot be considered to be an anhydride analogue in the present sense.

So far only the reactions of wholly carboxylic anhydrides and their analogues have been discussed. There appears to be no marked reaction of salts of acyl phosphoric acids under the usual conditions, but this is not surprising since their negative charge would prevent approach of the attacking reagent. With neutral acyl phosphates such as (XIII; R = R′ = R″ = Me, or R = R′ = Ph·CH_2, R″ = Me) this objection does not arise and

(XIII)   (XIV)

in both these cases acylation of orthophosphate ions has been observed rather than dialkylphosphorylation. This is explicable in terms of the inherently greater tendency in acetyl phosphates for the C–O rather than the O–P bond to be broken, just as acetic acid is much weaker than dimethyl or dibenzyl hydrogen phosphate. With tetramethyl pyrophosphate (XIV; R = R′ = R″ = R‴ = Me) in aqueous sodium hydrogen carbonate, reaction again occurred, as indicated by the disappearance of orthophosphate ions, to give, presumably, the salt of unsymmetrical dimethyl pyrophosphate (XIV; R = R′ = Me, R″ = R‴ = H). This reaction might conceivably be regarded as a model of phosphate transfer in biological systems where the negative charges of adenosine-5′ triphosphate, for example, should be capable of being screened by chelation or in some other way as a result of its enzymic environment.

Experimental

Analytical Methods.—Estimation of labile acyl groups. A procedure slightly modified from that of Lipmann and Tuttle (*J. Biol. Chem.*, **1944**, **153**, 571), based on the formation of a purple-red complex from hydroxamic acids and Fe^{3+}, was employed: 3·5N-sodium hydroxide (0·4 ml.) was mixed with 4·0M-hydroxylamine hydrochloride (0·5 ml.), and the sample solution and additional water were added to a total vol. of 3·00 ml. After 10 min. at room temperature, a solution (3·0 ml.) of 0·063M-ferric chloride in N-hydrochloric acid was added. After a further 5 min. the colour was measured in a photo-electric absorptiometer with a green filter. A standard curve of optical density–concentration was prepared for each carboxylic anhydride. *iso*Propenyl acetate gave no colour under these conditions.

For estimation of the acyl phosphate content of a reaction solution, the unchanged carboxylic anhydride or anhydride analogue was first removed by ether. Sampling was carried out as rapidly as possible to avoid losses by hydrolysis.

Filtration of the precipitated solid was necessary in estimations of D-riboflavin-5′ acyl phosphates before measurement of the final colour. In this and all other cases, appropriate blanks were carried out.

Phosphorus estimation. The uptake of orthophosphate ions in reactions with various anhydrides was determined as the difference between the orthophosphate content by the Lowry and Lopez procedure (*J. Biol. Chem.*, **1946**, **162**, 421) and that originally present.

Total-phosphorus determinations were carried out by combusion of samples with perchloric–sulphuric acid, followed by estimation of the orthophosphate produced by Berenblum and Chain's method (*Biochem. J.*, **1938**, **32**, 295), except that, owing to their molybdate-sensitivity, combustion was not necessary in the case of acyl unsubstituted phosphates such as acetyl phosphate salts.

Riboflavin. The total riboflavin content was determined colorimetrically, with sodium D-riboflavin-5′ phosphate dihydrate as a standard.

Glycine estimation. The ninhydrin procedure of Moore and Stein (*J. Biol. Chem.*, 1948, **176**, 367) was employed.

Acylations.—General procedure. The following conditions were used in most of the experiments which were carried out in order to screeen various anhydrides and anhydride-like substances for their action on orthophosphate ions in aqueous solution: 0·016M-Disodium hydrogen phosphate (1 mol.) in M-sodium hydrogen carbonate was cooled thoroughly in ice and, with vigorous mechanical stirring, the anhydride (10 mols.) was added, if necessary, in solution in dimethylformamide. Samples were withdrawn for analysis at appropriate intervals in order to follow the course of the acylation, which was usually optimal after 60 min.

When 2M-aqueous pyridine was used instead of bicarbonate, the production of acyl phosphate was faster and more nearly complete (~10 min.).

Solutions approximately five times as concentrated were usually employed with substituted phosphates, but an amount of solid sodium hydrogen carbonate corresponding to the excess of anhydride employed had then to be added. The aqueous pyridine procedure was generally preferred. The following examples illustrate the preparative usefulness of the reaction.

Dilithium and disilver acetyl phosphates. (*a*) A suspension of potassium hydrogen carbonate (50 g.) in water (100 ml.) and 2·5M-dipotassium hydrogen phosphate (20 ml.) were well stirred together and cooled in ice to 1°. Acetic anhydride (48 ml.) and more 2·5M-phosphate solution (80 ml.) were then added dropwise, separately but simultaneously, during 30 min. After an additional 1—2 hours' stirring, 31% aqueous lithium acetate dihydrate (100 ml.) was slowly added, followed carefully by 4M-lithium hydroxide (*ca.* 85 ml.) until a sample diluted 5—10-fold had pH 8·0—8·5. During all these procedures the mixture was kept below 5°. The resulting turbid liquid was then filtered through Hyflo Supercel, on an ice-cooled Buchner flask. The clear filtrate (*ca.* 420 ml.) was then treated, with good agitation, with cold absolute ethanol (4 l.). After settling for 2 hr. at 0°, the dilithium acetyl phosphate was filtered off and washed with alcohol and then with ether, and dried *in vacuo*. The white powder (31 g.) so obtained was about 63% pure. The crude dilithium salt (15 g.) was dissolved in ice-cold water (700 ml.) and treated with 25% aqueous silver nitrate (*ca.* 50 ml., equiv. to the inorganic phosphate content of crude lithium salt). After settling at 0—5° the dirty yellow precipitate of silver phosphate was filtered off (ice-cooled Buchner flask). The clear filtrate was treated with 25% aqueous silver nitrate (215 ml.), previously cooled to 0°, with agitation, the apparatus being protected from bright light. After 2 hours' settling at 0°, the crystalline salt was filtered off and washed with ice-cold water (3 × 25 ml.), cold absolute alcohol (3 × 150 ml.) and dry ether (2 × 150 ml.). The disilver acetyl phosphate (18·1 g., 40%) was obtained as light-sensitive, white, crystals of about 96% purity (Found: Ag, 60·7; P, 8·75; labile acetyl, 11·65. Calc. for $C_2H_3O_5PAg_2$: Ag, 61·0; P, 8·75; Ac, 12·1%).

(*b*) Pyridine (95 g. 1·2 moles) and 0·25M-dipotassium hydrogen phosphate (200 ml.) were stirred together at 0° to give a clear, single phase. Acetic anhydride (9·6 ml., 0·1 mole) was then added dropwise to the vigorously stirred solution during 5 min., causing the temperature to rise to 3·5°. After 35 min., 4·1N-lithium hydroxide (37 ml.) was added, giving (after 10-fold dilution with water) a practically clear solution of pH 7·6: 90% conversion was observed at this stage. Cold ethanol (2300 ml.) was then added slowly, and the precipitate allowed to settle for 2 hr. at 0° before being filtered off. Crude dilithium acetyl phosphate (6·85 g., containing 32·5 mmoles of labile acetyl) was obtained.

Sodium D-*riboflavin-5′ acetyl phosphate.* Monosodium D-riboflavin-5′ phosphate dihydrate (340 mg., 0·66 mmole) was dissolved in 40% aqueous pyridine (8 ml.), and the solution cooled to 0°. With vigorous stirring, acetic anhydride (0·33 ml., 3·4 mmoles) was added. After 5 min., ice-cold acetone (50 ml.) was added, and the precipitated product rapidly filtered off, washed with cold acetone and then dry ether, and dried rapidly *in vacuo*. The sodium D-riboflavin-5′ acetyl phosphate was obtained as an orange solid (330 mg.) of about 90% purity (Found : riboflavin, 63; labile acetyl, 6·45. Calc. for $C_{19}H_{22}O_{10}N_4PNa,4H_2O$: riboflavin, 63; Ac, 7·25%). It is stable for long periods at $<0°$ in the absence of light and moisture but decomposes slowly at room temperature.

Sodium D-*riboflavin-5′ chloroacetyl phosphate.* Monosodium D-riboflavin-5′ phosphate dihydrate (170 mg., 0·33 mmole) was dissolved in 40% aqueous pyridine (4 ml.), the solution cooled to 0°, and, with vigorous stirring, a solution of chloroacetic anhydride (560 mg. 3·3 mmoles) in dry acetonitrile (3 ml.) was added, half at once and the remainder dropwise during the next 5 min. Then cold acetone (25 ml.) was at once added, and the product isolated as for the corresponding acetyl compound. The orange solid (137 mg.) so obtained contained *ca.* 80% of sodium D-riboflavin-5′ chloroacetyl phosphate (Found : riboflavin, 65; labile $CH_2Cl{\cdot}CO$, 10·8. Calc. for $C_{19}H_{21}O_{10}N_4ClPNa,2H_2O$: riboflavin, 64; $CH_2Cl{\cdot}CO$, 13·1%). The impurity in both the above preparations was the unacylated compound. The chloroacetyl compound was even less stable than the acetyl compound, but it could be stored safely at $-10°$, at least for several days. The dry solid lost 20% of its content of the chloroacetyl compound in 5 hr. at 20°.

Reaction of Ethoxycarbonylaminoacetyl Ethyl Carbonate (IV) *with Orthophosphate Ions.*—A procedure based on those of Wieland *et al.* (*Annalen*, 1951, **573**, 99), Vaughan (*J. Amer. Chem. Soc.*, 1951, **73**, 3547), and Boissonas (*Helv. Chim. Acta*, 1951, **34**, 874) was used. *N*-Ethoxycarbonylglycine (3·7 g., 25 mmoles) was dissolved in dry acetonitrile (15 ml.), and triethylamine (2·5 g., 25 mmoles) was added. To this, cooled in ice–salt, with good stirring, ethyl chloroformate (2·7 g., 25 mmoles) in dry acetonitrile (5 ml.) was added dropwise. Triethylamine hydrochloride was soon precipitated and, after the halide addition was complete, the mixture was stored in ice–salt for 30 min. before use. This solution was used to acylate sodium phosphate (2·5 mmoles) in M-potassium hydrogen carbonate (40 ml.). Under these conditions the conversion was *ca.* 35% after 2 hr.

Reaction of 2-Phenyl-5-oxazolone (IX; R = Ph, R′ = H) *with Phosphate Ions.*—2-Phenyloxazolone (0·645 g., 4·0 mmoles) was added to disodium hydrogen phosphate (2·0 mmoles) in 16% aqueous pyridine (20 ml.) at 0°. Complete conversion of the orthophosphate into *N*-benzoylglycyl phosphate (X) occurred in 90 min.

Reaction of Benzoylglycyl Phosphate (X) *with Aniline.*—Aniline (10 mols.) was incubated with an ether-washed portion of the above solution of hippuryl phosphate (1 mol.) at 37° for 1 hr. The resulting white solid (56%) had m. p. 217—218°, undepressed on mixing with a pure, authentic specimen of benzoylglycine anilide (m. p. 217—218°).

Reaction of 4-Benzyl-2-methyl-5-oxazolone (IX; R = Me, R′ = CH_2Ph) *with Phosphate Ions.*—The azlactone (0·76 g., 4·0 mmoles) was added to sodium phosphate (2·0 mmoles) in 32% aqueous pyridine (20 ml.) at 0° with vigorous stirring, converting 93% of the phosphate ions into the product (XI) in 1 hr.

Reaction of α-Acetamido-β-phenylpropionyl Phosphate with Glycine.—The foregoing solution was washed with ether to remove any unchanged azlactone, and glycine (150 mg. 2·0 mmoles), dissolved in a little M-sodium hydrogen carbonate, was added. The solution was brought to pH 8·4 with N-sodium hydroxide, and M-sodium hydrogen carbonate (6 ml.) was then added to buffer the solution to pH 8·2. It was divided into two parts, one of which was stored at 1°, and the other at room temperature. After 72 hr., no change in the glycine content of either solution had occurred. All the original acyl phosphate (XI) had disappeared from the solution after 72 hr. at room temperature, while 50% of it remained in the refrigerated solution.

In a similar experiment, the phosphate also did not react with glycine.

Reaction of the Azlactone (IX; R = Me, R′ = CH_2Ph) *with Adenosine-5′ Phosphate.*—Synthetic adenosine-5′ phosphoric acid (245 mg., 0·7 mmole) was dissolved in 32% aqueous pyridine (7 ml.), and the azlactone (265 mg., 1·4 mmoles) added with vigorous stirring at 0°. After 1 hr. a portion (2 ml.) was analysed and 81% conversion of the adenylic acid into (XII) was found. This value was unchanged after a further 30 min.

Reaction of N-Acetylphenylalanyl Phosphate (XII) *with Glycine.*—The remaining solution of (XII) (containing *ca.* 0·4 mmole) was washed with ether and treated with glycine (37·5 mg., 0·5 mmole) and buffered as before to pH 8·2. The mixture was then allowed to remain at

room temperature for 1 hr.; by then all the reactant (XII) had disappeared and only 65% of the glycine (0·325 mmole) remained. The solution was acidified with 85% phosphoric acid (0·5 ml.), and the acylamino-acid and acylpeptide products were extracted with ethyl acetate (cf. Kenner and Stedman, *J.*, 1952, 2069). Concentration of the extract gave a residue (90 mg.) which was dissolved in water and subjected to paper chromatography in *n*-butanol saturated with 2N-ammonia (Kenner and Stedman, *loc. cit.*). This enabled the two components to be identified as *N*-acetylphenylalanine and *N*-acetylphenylalanylglycine.

Acetyl Dibenzyl Phosphate (XIII; R = R′ = CH_2Ph, R″ = Me).—A suspension of silver dibenzyl phosphate in ether was treated with acetyl chloride (cf. Lynen, *Ber.*, 1940, 73, 367), and the resulting ethereal solution of acetyl dibenzyl phosphate (after filtration of silver halide) was concentrated and used directly.

Acetyl Dimethyl Phosphate (XIII; R = R′ = R″ = Me).—Trimethyl phosphate and an equivalent amount of 2N-sodium hydroxide in 60—90 min. at 60° gave sodium dimethyl phosphate (hydrolysis followed by titration of aliquot portions at intervals). The sodium salt was converted into the triethylammonium salt by passage of the hydrolysis solution, diluted with water to 0·067M, down a column of Amberlite IRC-50 in the triethylammonium form, concentration of the aqueous effluent *in vacuo*, and drying of the residue by evaporation with benzene. The dry, syrupy triethylamine salt (1 mol.) was suspended in dry ether and treated with acetyl chloride (1·5 mols.) at 0°. The resulting ethereal solution of acetyl dimethyl phosphate was filtered under anhydrous conditions from the base hydrochloride and concentrated *in vacuo*. The resulting viscous oil had a purity of 80—90% and was stored at 0° before use.

Reactions of Neutral Acyl Phosphates with Phosphate Ions.—The reactions of the phosphates (XIII; R = R′ = CH_2Ph, R″ = Me; and R = R′ = R″ = Me) with sodium phosphate under the usual conditions (aqueous bicarbonate or aqueous pyridine) were followed analytically by the methods of Lowry and Lopez and of Berenblum and Chain (*locc. cit.*), as well as by the labile acetyl determinations on the ether-washed solutions. These showed that orthophosphate ions are acylated, but not dialkylphosphorylated, by acetyl dialkyl phosphates.

Acetyl dimethyl phosphate was also found to acetylate the phosphate group of sodium D-riboflavin-5′ phosphate.

Reaction of Tetramethyl Pyrophosphate with Phosphate Ions.—Tetramethyl pyrophosphate (Toy, *J. Amer. Chem. Soc.*, 1949, 71, 2268) (1·6 g., 6·8 mmoles) was added to sodium phosphate (0·67 mmoles) in M-sodium hydrogen carbonate (40 ml.) vigorously stirred at 0°. As indicated by estimations of phosphate, about 25% of the orthophosphate ions were converted into *PP*-dimethyl dihydrogen pyrophosphate (XIV; R = R′ = Me, R″ = R‴ = H) in 1 hr. However, hydrolysis supervened to a detectable extent after 2—3 hr., even at 0°. When aqueous pyridine was used as reaction medium, the maximum conversion was only *ca.* 10% and, on warming to room temperature, hydrolysis was complete in 30 min. It is, of course, to be expected that an unsymmetrical dialkyl pyrophosphate should have somewhat the same hydrolytic stability as an acyl phosphate, and it appears that, whereas the hydrolysis is pyridine-catalysed, the synthesis is not (cf. proposed reaction mechanism).

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2 : 3-*Dihydro*-3-*oxobenz*-1 : 4-*oxazines*.

By J. D. Loudon and J. Ogg.

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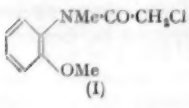
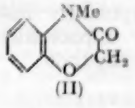
The action of aluminium chloride on α-chloroacyl-*o*-anisidides leads to 2 : 3-dihydro-3-oxobenz-1 : 4-oxazines and, in some cases, thence or directly to hydroxyoxindoles. Some reactions of the benzoxazines are described. The action of aluminium chloride on β-chloro-propion-*o*-anisidide and -*N*-methylpropion-*o*-anisidide, leading to 3 : 4-dihydrocarbostyrils, is examined. A satisfactory preparation of 2 : 4-dimethoxynitrobenzene is given.

It was shown by Cook, Loudon, and McCloskey (*J.*, 1952, 3904) that heating α-chloro-*N*-methylacet-*o*-anisidide (I) with aluminium chloride leads to the benzoxazine derivative (II) which at higher temperatures is rearranged to a mixture of 7- and 4-hydroxy-1-methyloxindole, (III) and (IV) respectively. The mixture was not separated into its components as such but, after methylation, the individual ethers were isolated and identified by independent syntheses. Almost at the same time Kretz, Muller, and Schlittler (*Helv. Chim. Acta*, 1952, 527) reported that the action of aluminium chloride on (I) gave much of (II) together with a hydroxy-1-methyloxindole which they regarded as (III). This conclusion, which overlooks the simultaneous formation of (III) and (IV), is obviously unsound and is, in fact, erroneous. The phenolic compounds (III) and (IV) are readily prepared by demethylation of their *O*-methyl ethers and we find that the properties of Kretz, Muller, and Schlittler's compound correspond with those of 4-hydroxy-1-methyloxindole (IV) and differ from those of (III).



(I)



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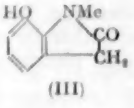

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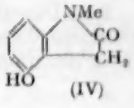
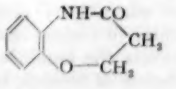
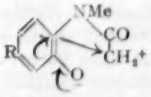


(IV)

(V)





(VI)

The formation of benzoxazine derivatives from chloroacet-*o*-anisidides by reaction with aluminium chloride appears to be general. It proceeds through demethylation to *o*-chloroacetamidophenols which, in the absence of an *N*-alkyl substituent, are frequently isolatable and yield the benzoxazines by dissolution in aqueous alkali. A number of examples are described in the Experimental section. On the other hand, *o*-β-chloropropionamidophenol, obtained by demethylating β-chloropropion-*o*-anisidide, reacted with aqueous alkali to give a product which is regarded as *o*-acrylamidophenol rather than the isomeric 7-membered ring compound (V). This conclusion is based on the solubility of the product in alkali, on its ability to absorb 1 mol. of hydrogen and, more especially, on the similarity of the ultra-violet spectra obtained in presence and absence of alkali.

2 : 3-Dihydro-3-oxobenz-1 : 4-oxazine (II; H for Me) is readily *N*-methylated by methyl sulphate and alkali but, in general, methylation is best achieved by using methyl iodide and powdered potassium hydroxide in acetone (cf. Pachter and Kloetzal, *J. Amer. Chem. Soc.*, 1952, **74**, 1321). Both the parent compound and its *N*-methyl derivative (II) contain reactive—albeit feebly reactive—methylene groups as is shown by the formation of benzylidene derivatives. As a cyclic amide, (II) is readily reduced by lithium aluminium hydride, forming 2 : 3-dihydro-4-methylbenz-1 : 4-oxazine. The convertibility of 2 : 3-dihydro-3-oxobenzoxazines into hydroxyoxindoles is restricted in practice by the high temperature (200—220°) required for the reaction and also by the need for a 4(*N*)-substituent. Thus we have confirmed (cf. Cook *et al.*, *loc. cit.*) that neither 2 : 3-dihydro-3-oxobenz-1 : 4-oxazine nor its 2-methyl derivative yields oxindoles in appreciable amount, whereas (II) yields (III) and (IV), and 2 : 3-dihydro-2 : 4-dimethyl-3-oxobenz-1 : 4-oxazine

affords 7-hydroxy-1 : 3-dimethyloxindole. In this last reaction no isomeric product, corresponding to the transformation of (II) into (IV), was detected and the structure of the isolated product was established by its conversion into 7-methoxy-1 : 3-dimethylindole which was independently synthesised. If the change from (II) to (IV) involves the mechanism briefly indicated by (VI), it should be promoted where the substituent R is an electron-donor. However, 2 : 3-dihydro-7-hydroxy-4-methyl-3-oxobenz-1 : 4-oxazine, which was synthesised to test this view, proved to be too unstable under the conditions for isomerisation. Thereby, like its 6-hydroxy-isomer and also like 2 : 3-dihydro-4-methyl-3-oxonaphth(2′ : 1′-2 : 3)-1 : 4-oxazine (cf. Lees and Shedden, *J.*, 1903, **83**, 758), it was converted into an intractable, highly coloured, and amorphous powder.

Under favourable conditions the hydroxyoxindoles (III) and (IV) are directly produced by the action of aluminium chloride on (I) without isolation, and possibly without intermediate formation, of the benzoxazine (II). The reaction is thus a particular case of Stollé's oxindole synthesis (*J. pr. Chem.*, 1930, **128**, 1; cf. Abramovitch and Hey, *J.*, 1954, 1697) which is known to give optimum results when the α-chloroacylaniline used carries an *N*-alkyl substituent (see Julian in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1952, Vol. III, p. 144). On the other hand, 3 : 4-dihydrocarbostyrils are readily prepared by the action of aluminium chloride at relatively low temperatures on β-chloropropionanilides whether *N*-alkylated or not (Mayer, Zütphen, and Philipps, *Ber.*, 1927, **60**, 858). The latter reaction was therefore examined with the β-chloropropionyl derivatives of *o*-anisidine and *N*-methyl-*o*-anisidine. In each case a single product was obtained and was identified as 3 : 4-dihydro-8-hydroxycarbostyril and its *N*-methyl derivative respectively. For identification, the products, after *O*-methylation and reduction, were converted into suitable derivatives of 1 : 2 : 3 : 4-tetrahydro-8-methoxyquinoline.

2 : 4-Dimethoxynitrobenzene, hitherto surprisingly inaccessible, was prepared from resorcinol dimethyl ether either by successive sulphonation and nitration or, better, by direct nitration using copper nitrate in acetic anhydride.

Experimental

General Procedures.—*N*-Acylation of amines was effected by adding the acid chloride (0·1 mole) slowly to a cooled, stirred solution of the amine (0·1 mole) and pyridine (0·1 mole) in benzene (500 c.c.), and after 24 hr. at room temperature the amide was recovered from the acid-washed, dried, benzene solution. For *N*-methylation of amides, both cyclic and acyclic, methyl iodide (0·15 mole) was added in two portions (10-min. interval) to a gently boiling suspension of powdered potassium hydroxide (0·25 mole) in acetone (350 c.c.; "AnalaR") containing the amide (0·1 mole); heating was continued for 20 min. and the product was recovered by concentrating the solution and adding water (cf. Pachter and Kloetzal, *loc. cit.*). Preferential *O*-methylation of phenolic amides was similarly effected by using potassium carbonate (0·25 mole) in place of the hydroxide and heating under reflux for 6 hr. Fusion with aluminium chloride was carried out by heating the mixed, powdered reagents with stirring at the temperature and for the time stated, followed by decomposition of the cooled, powdered product with iced hydrochloric acid and subsequent treatment as described.

2 : 3-Dihydro-3-oxobenz-1 : 4-oxazine, m. p. 171—172° (from water), was prepared (*a*) by hydrogenating *o*-nitrophenoxyacetic acid (Minton and Stephen, *J.*, 1922, **121**, 1591) in acetic acid with palladium as catalyst, being obtained almost quantitatively from the filtered and concentrated solution; (*b*) by fusing chloroacet-*o*-anisidide with aluminium chloride at 180° for 1 hr. (cf. Cook, Loudon, and McCloskey, *loc. cit.*). By the latter procedure at a lower temperature (80—100°; 30 min.) the main product was *o*-chloroacetamidophenol, m. p. 135·5—136·5° (from benzene) (Found: C, 51·4; H, 4·3; N, 7·7. Calc. for $C_8H_8O_2NCl$: C, 51·8; H, 4·3; N, 7·55%) (Aschan, *Ber.*, 1887, **20**, 1524, gives m. p. 136° for the compound as prepared from *o*-aminophenol), and this by dissolution in alkali was converted into the oxazine. Moreover, when the pre-formed oxazine was fused with aluminium chloride at 220° for 20 min. it afforded a solid, m. p. 114—115° (from water) (Found: C, 57·3; H, 5·0%), which appears to be a mixture of *o*-chloroacetamidophenol and unchanged oxazine since it (i) had mixed m. p. 125—128° with the former compound and (ii) gave the oxazine, m. p. 167—171°, when recovered by evaporation from 2N-hydrochloric acid. Auwers and Fries (*Ber.*, 1926, **59**, 539) obtained a similar product, m. p. 114—115°, which they regarded as an allotropic modification of *o*-chloro-

acetamidophenol, by the action of chloroacetyl chloride on *o*-aminophenol in weakly alkaline solution (wherein some formation of the oxazine is to be expected).

2 : 3-Dihydro-3-oxobenz-1 : 4-oxazine had light absorption (in EtOH) : $\lambda_{max.}$ 2550, 2860 Å (log ε, 3·73, 3·59). It is slightly soluble in aqueous alkali and yields the 4-methyl derivative (see below) by treatment with methyl sulphate in sodium hydroxide. When it (1·5 g.) was heated (8 hr.) with benzaldehyde (1·1 g.) and acetic anhydride (3·1 g.) in presence of fused sodium acetate, and the whole was then added to water, the recovered oil afforded as neutral fraction 2-*benzylidene*-2 : 3-*dihydro*-3-*oxobenz*-1 : 4-*oxazine* which formed pale yellow needles, m. p. 260—261° (from ethanol) (Found : C, 75·9; H, 5·0; N, 6·2. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·7; N, 5·9%) : light absorption (in EtOH), $\lambda_{max.}$ 2570, 3350 Å (log ε 4·19, 4·29). Catalytic hydrogenation of this compound in acetic acid with palladium as catalyst afforded 2-*benzyl*-2 : 3-*dihydro*-3-*oxobenz*-1 : 4-*oxazine*, m. p. 159° (from light petroleum, b. p. 60—80°) (Found : C, 74·8; H, 4·9; N, 6·1. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·85%) : light absorption (in EtOH) : $\lambda_{max.}$ 2520, 2810 Å (log ε 3·83, 3·66).

2 : 3-Dihydro-4-methyl-3-oxobenz-1 : 4-oxazine, m. p. 58° (from light petroleum, b. p. 60—80°), was prepared (*a*) in 90% yield by *N*-methylation of the foregoing oxazine; (*b*) as described by Cook, Loudon, and McCloskey (*loc. cit.*) from anisidine—but by the general procedures given here—*via* α-*chloro*-N-*methylacet*-o-*anisidide* which was now obtained as rods, m. p. 49—50° (from light petroleum, b. p. 40—60°) (Found : C, 56·35; H, 5·5. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·7%), and afforded the oxazine, m. p. 57—58°, when fused with aluminium chloride at 180° for 1 hr. The oxazine had light absorption (in EtOH) : $\lambda_{max.}$ 2540, 2850 Å (log ε 3·78, 3·64). It (0·8 g.) condensed with benzaldehyde (0·53 g.) when they were heated (12 hr.) together in benzene (25 c.c. in presence of powdered sodamide (0·3 g.) affording 2-*benzylidene*-2 : 3-*dihydro*-4-*methyl*-3-*oxobenz*-1 : 4-*oxazine* as yellow needles, m. p. 155—156° (from ethanol) (Found : C, 76·2; H, 5·35; N, 5·8. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%) : light absorption (in EtOH) : $\lambda_{max.}$ 2700, 3370 Å (log ε 4·15, 4·28). The corresponding benzyl compound, as prepared by catalytic hydrogenation, did not solidify.

2 : 3-Dihydro-4-methylbenz-1 : 4-oxazine, b. p. 61°/5 × 10^{-6} mm. (Knorr, *Ber.*, 1889, **22**, 2081, gives b. p. 261°/760 mm.), was obtained when the foregoing 3-oxo-derivative (5 g.) and lithium aluminium hydride (2 g.) were allowed to react in anhydrous ether (200 c.c.) during 3 days and the washed and dried ether solution was evaporated. It formed a *picrate*, m. p. 149—150° (from ethanol) (Found : C, 47·7; H, 4·0; N, 14·95. $C_9H_{11}ON,C_6H_3O_7N_3$ requires C, 47·6; H, 3·7; N, 14·8%), a hydrochloride, m. p. 168—169° (from ethanol) (Found : C, 58·3; H, 6·25; N, 7·6. Calc. for $C_9H_{11}ON,HCl$: C, 58·2; H, 6·5; N, 7·55%), and a methiodide, m. p. 198—200° (decomp.) (from methanol). For the last two derivatives Lees and Shedden (*loc. cit.*) give m. p.s 167—167° and 195—200°, respectively. Light absorption of the hydrochloride (in EtOH) : $\lambda_{max.}$ 2580, 2980 Å (log ε 3·82, 3·56).

4- *and* 7-*Hydroxy*-1-*methyloxindole*.—α-Chloro-*N*-methylacet-*o*-anisidide (3 g.) was fused with anhydrous aluminium chloride (4 g.) at 220° for 1 hr. and the phenolic products (2·1 g.) were *O*-methylated in acetone, affording a mixture of 4- and 7-methoxy-1-methyloxindole, which was purified by distillation and separated by preferential extraction of the latter isomer in ether (cf. Cook *et al.*, *loc. cit.*). Light absortion (in EtOH) of 4-methoxy-1-methyloxindole (m. p. 137°), $\lambda_{max.}$ 2510, 2810 Å (log ε 3·67, 3·32); of 7-methoxy-1-methyloxindole (m. p. 102°), $\lambda_{max.}$ 2530, 2950 Å (log ε, 3·95, 3·50). When fused with aluminium chloride (0·4 g.) at 120° for 30 min. the 4-methoxy-isomer (0·2 g.) afforded 4-*hydroxy*-1-*methyloxindole*, m. p. 230—232° (from water) : light absorption (in EtOH) : $\lambda_{max.}$ 2520, 2800 Å (log ε 3·83, 3·37) (Found : C, 66·1; H, 5·5. $C_9H_9O_2N$ requires C, 66·2; H, 5·6%). Similarly the 7-methoxy-isomer gave 7-*hydroxy*-1-*methyloxindole*, m. p. 275—277°; light absorption (in EtOH) : $\lambda_{max.}$ 2450, 2860 Å (log ε 3·82, 3·52) (Found : C, 66·0; H, 5·6%). The former hydroxy-isomer corresponds in m. p. with that (m. p. 227—228°) recorded by Kretz, Muller, and Schlittler (*loc. cit.*), and of the two isomers it alone gave a dye of the rhodamine type when fused with phthalic anhydride and zinc chloride.

2 : 3-*Dihydro*-2 : 4-*dimethyl*-3-*oxobenz*-1 : 4-*oxazine*.—α-Chloropropion-*o*-anisidide (34 g.), obtained as a light yellow oil from *o*-anisidine and α-chloropropionyl chloride, was fused with aluminium chloride (30 g.) at 120° (30 min.). The phenolic product was dissolved in dilute aqueous sodium hydroxide (250 c.c.) from which 2 : 3-dihydro-2-methyl-3-oxobenz-1 : 4-oxazine crystallised as needles, m. p. and mixed m. p. 143—144° (from benzene) (cf. Cook *et al.*, *loc. cit.*). *N*-Methylation of this oxazine afforded 2 : 3-*dihydro*-2 : 4-*dimethyl*-3-*oxobenz*-1 : 4-*oxazine* also as needles, m. p. 49·5—50° (from light petroleum, b. p. 40—60°) (Found : C, 67·5; H, 6·0. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3%). Light absorption (in EtOH) : $\lambda_{max.}$ 2550, 2860 Å (log ε 4·01, 3·9).

7-*Hydroxy*-1 : 3-*dimethyloxindole*.—**2 : 3**-Dihydro-**2 : 4**-dimethyl-**3**-oxobenz-**1 : 4**-oxazine (5 g.) was fused with aluminium chloride (10 g.) at 220° (1 hr.) and the phenolic product (4·5 g.), after purification in methanol on a charcoal column, gave **7-*hydroxy*-1 : 3-*dimethyloxindole*** as prisms, m. p. 224—226° (from methanol) (Found: C, 67·6; H, 6·6; N, 7·55. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). Light absorption (in EtOH): $\lambda_{max.}$ 2490, 2970 Å (log ε 3·87, 3·57). The oil obtained by *O*-methylation of this compound in acetone was distilled at 146—148°/9·8 × 10^{-2} mm., affording a solid distillate of **7-*methoxy*-1 : 3-*dimethyloxindole***, needles, m. p. 65—66° (from light petroleum, b. p. 40—60°) (Found: C, 68·9; H, 6·55; N, 7·5. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). Light absorption (in EtOH): $\lambda_{max.}$ 2520, 2930 Å (log ε, 3·92, 3·5).

7-*Methoxy*-1 : 3-*dimethylindole*.—(*a*) The foregoing oxindole (0·5 g.) was reduced (5 hr. at room temperature) with lithium aluminium hydride (0·2 g.) in dry ether (25 c.c.). The solid obtained, after being washed first with water, then with dilute hydrochloric acid and recovered by evaporation of the dried ethereal layer, afforded **7-*methoxy*-1 : 3-*dimethylindole*** as rhombs, m. p. 68—69° (from light petroleum, b. p. 40—60°) (Found: C, 75·5; H, 7·1; N, 8·65. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5; N, 8·0%). Light absorption (in EtOH): $\lambda_{max.}$ 2260, 2730, 2880, 3000 Å (log ε 4·69, 3·74, 3·78, 3·78). The compound, which gave a positive Ehrlich reaction, formed a ***picrate*** as chocolate-brown needles, m. p. 163—164° (from ethanol) Found: C, 50·3; H, 3·8; N, 14·1. $C_{11}H_{13}ON,C_6H_3O_7N_3$ requires C, 50·5; H, 4·0; N, 13·9%). The acid washings of the foregoing ethereal extract, after basification, recovery in ether, and addition of an ethereal solution of picric acid, afforded **7-*methoxy*-1 : 3-*dimethylindoline picrate*** as yellow plates, m. p. 135—136° (from ethanol) (Found: C, 50·6; H, 4·8; N, 13·95. $C_{11}H_{15}ON,C_6H_3O_7N_3$ requires C, 50·25; H, 4·5; N, 13·8%).

(*b*) A solution of 7-methoxy-3-methylindole (1·2 g.) (Cook *et al.*, *loc. cit.*) in ether (10 c.c.) was slowly added with stirring at −40° to a solution of potassium (0·29 g.) in liquid ammonia (*ca.* 25 c.c.) containing a crystal of ferric nitrate. Then methyl iodide (1·1 g.) in ether (10 c.c.) was added and, after 45 min. at −40°, the solvent was allowed to evaporate, and the residue in light petroleum (b. p. 40—60°) was passed through a column of alumina; the early eluate afforded 7-methoxy-1 : 3-dimethylindole, m. p. and mixed m. p. with the previous sample 69—70° (picrate, m. p. and mixed m. p. 162—163°).

2 : 4-*Dimethoxynitrobenzene*.—(*a*) Concentrated sulphuric acid (20 c.c.) was slowly added to a solution of resorcinol dimethyl ether (20 g.) in acetic acid (100 c.c.), and the whole was then warmed to 70° to complete the reaction. The cooled solution was diluted with water (20 c.c.), treated with concentrated nitric acid (20 c.c.; *d*, 1·42), and left overnight at room temperature. Water (750 c.c.) was added and the whole was extracted with benzene, the extract being washed with dilute sodium hydroxide solution, dried, and passed through a column of alumina, from which the product was readily eluted. 2 : 4-Dimethoxynitrobenzene was recovered from the eluate as colourless plates, m. p. 74° (30% yield).

(*b*) Resorcinol dimethyl ether (10 g.) was slowly stirred into a mixture of copper nitrate (10 g.) and acetic anhydride (30 g.) kept below 25°. After 4 hr. the whole was added to water (300 c.c.) and the resultant solid was collected and purified as in (*a*) (70% yield).

2 : 3-*Dihydro*-7-*hydroxy*-3-*oxobenz*-1 : 4-*oxazine*.—**2 : 4**-Dimethoxyaniline was obtained as a colourless oil, b. p. 75—80°/6 × 10^{-3} mm., by hydrogenating **2 : 4**-dimethoxynitrobenzene in acetic acid with palladium as catalyst. The derived α-chloro-**2 : 4**-dimethoxyacetanilide (2 g.), m. p. 90° (Heidelberger and Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 1469, give m. p. 90°), when fused with aluminium chloride (10 g.) and sodium chloride (4 g.) at 140° (15 min.), afforded ***α-chloro*-2 : 4-*dihydroxyacetanilide***, m. p. 179—180° (from water) (Found: C, 47·9; H, 4·3; N, 7·3. $C_8H_8O_3NCl$ requires C, 47·7; H, 4·0; N, 7·0%). This compound was dissolved in dilute sodium hydroxide solution and after 1 hr. the solution was acidified, saturated with ammonium sulphate, and extracted with ether, from which **2 : 3-*dihydro*-7-*hydroxy*-3-*oxobenz*-1 : 4-*oxazine*** was recovered and formed colourless needles, m. p. 208—209° (from water) (Found: C, 58·2; H, 4·5; N, 8·6. $C_8H_7O_3N$ requires C, 58·2; H, 4·3; N, 8·5%). Light absorption (in EtOH): $\lambda_{max.}$ 2680 Å; log ε, 3·91; inflexion, 2840—2920 Å (log ε 3·77—3·72). In ice-cold dilute sodium hydroxide it reacted with acetic anhydride, forming the **7-*acetoxy*-**derivative, m. p. 216—217° (from water) (Found: C, 58·0; H, 4·2; N, 6·8. $C_{10}H_9O_4N$ requires C, 58·0; H, 4·4; N, 6·8%).

2 : 3-*Dihydro*-7-*hydroxy*-4-*methyl*-3-*oxobenz*-1 : 4-*oxazine*.—**2 : 4**-Dimethoxy-*N*-methylacetanilide, obtained as an oil by *N*-methylation of **2 : 4**-dimethoxyacetanilide (the latter had m. p. 116°; Vermeulen, *Rec. Trav. chim.*, 1919, **38**, 109, gives m. p. 117°), was hydrolysed by hot 30% sulphuric acid, affording **2 : 4**-dimethoxy-*N*-methylaniline, b. p. 66—68°/3 × 10^{-4} mm., and this was characterised as the ***benzoyl*** derivative, m. p. 173—174° (from ethanol) (Found:

C, 70·6; H, 6·0; N, 5·3. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%). The corresponding chloroacetyl derivative was solid at 0° but without purification it (2 g.) was fused with aluminium chloride (10 g.) and sodium chloride (4 g.) at 140° (½ hr.) affording, after recovery, **2 : 3-*dihydro*-7-*hydroxy*-4-*methyl*-3-*oxobenz*-1 : 4-*oxazine*** as needles, m. p. 180—182° (from water : charcoal) (Found : C, 60·6; H, 5·3; N, 8·1. $C_9H_9O_3N$ requires C, 60·3; H, 5·1; N, 7·8%). Light absorption (in EtOH) : $\lambda_{max.}$ 2640, 2890 Å (log ε 3·90, 3·78).

2 : 3-*Dihydro*-6-*hydroxy*-3-*oxobenz*-1 : 4-*oxazine*.—**α-*Chloro*-2 : 5-*dimethoxyacetanilide***, m. p. 76—77° (from light petroleum, b. p. 60—80°), was prepared from 2 : 5-dimethoxyaniline and chloroacetyl chloride (Found : C, 53·1; H, 5·0; N, 6·4. $C_{10}H_{12}O_3NCl$ requires C, 52·4; H, 5·3; N, 6·1%). It was also regenerated, by the action of ethereal diazomethane, from **α-*chloro*-2 : 5-*dihydroxyacetanilide***, m. p. 196—197° (from water) (Found : C, 47·8; H, 3·9; N, 6·9. $C_8H_8O_3NCl$ requires C, 47·7; H, 4·0; N, 6·95%), to which it gave rise when heated with aluminium chloride and sodium chloride at 140° (10 min.). When the dihydroxy-compound was just brought into solution in dilute aqueous sodium hydroxide a transient green colour appeared and changed to brown while a brown solid was deposited. This solid was collected and combined with material recovered in ether from the acidified solution, affording **2 : 3-*dihydro*-6-*hydroxy*-3-*oxobenz*-1 : 4-*oxazine*** as colourless needles, m. p. 249—250° (from water : charcoal) (Found : C, 58·3; H, 4·4; N, 8·2. $C_9H_7O_3N$ requires C, 58·2; H, 4·3; N, 8·5%). Light absorption (in EtOH) : $\lambda_{max.}$ 3020 Å (log ε 3·69); inflexion, 2500—2600 Å (log ε 3·54—3·48). It afforded the **6-*acetoxy*-**derivative, m. p. 162° (from water) (Found : C, 58·6; H, 4·7; N, 6·9. $C_{10}H_9O_4N$ requires C, 58·0; H, 4·4; N, 6·8%), but attempted *O*-methylation gave the *ON*-dimethyl derivative, m. p. and mixed m. p. 76—77° (see below).

2 : 3-*Dihydro*-6-*hydroxy*-4-*methyl*-3-*oxobenz*-1 : 4-*oxazine*.—2 : 5-Dimethoxy-*N*-methylaniline, b. p. 70°/1·8 × 10^{-4} mm., obtained from 2 : 5-dimethoxyacetanilide by *N*-methylation and subsequent hydrolysis, reacted with chloroacetyl chloride forming **α-*chloro*-2 : 5-*dimethoxy*-N-*methyl*-*acetanilide***, m. p. 67—68° (from light petroleum, b. p. 40—60°) (Found : C, 54·5; H, 5·4; N, 6·2. $C_{11}H_{14}O_3NCl$ requires C, 54·3; H, 5·75; N, 5·8%). This compound (1 g.) was fused with aluminium chloride (5 g.) and sodium chloride (2 g.) at 140° (15 min.), affording **2 : 3-*dihydro*-6-*hydroxy*-4-*methyl*-3-*oxobenz*-1 : 4-*oxazine*** as colourless needles, m. p. 209° (from water) (Found : C, 60·4; H, 4·9; N, 8·0. $C_9H_9O_3N$ requires C, 60·3; H, 5·1; N, 7·8%). Light absorption (in EtOH) : $\lambda_{max.}$ 3030 Å (log ε 3·72), inflexion, 2500—2600 Å (log ε 3·58—3·46). On acetylation it formed the **6-*acetoxy*-**derivative, m. p. 93—94° (from water) (Found : C, 59·6; H, 4·7; N, 6·6. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%), and on methylation gave the **6-*methoxy*-**derivative, m. p. 77—78° (from light petroleum, b. p. 60—80°) (Found : C, 62·5; H, 5·7; N, 7·5. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·25%). Light absorption for the 6-methoxy-compound (in EtOH) : $\lambda_{max.}$ 3000 Å (log ε, 3·73); inflexion, 2440—2580 Å (log ε 3·60—3·50).

2 : 3-*Dihydro*-5-*methyl*-3-*oxobenz*-1 : 4-*oxazine*.—Chloroacetic acid (14·6 g.) was added to a boiling solution of 2-nitro-***m***-cresol (21·5 g.) and sodium hydroxide (12·4 g.) in water (200 c.c.) and, after 3 hr. at 100°, unchanged nitrocresol was removed in steam. Acidification of the residual solution afforded **3-*methyl*-2-*nitrophenoxyacetic acid***, m. p. 194—196° (from water) (Found : C, 51·45; H, 4·3. $C_9H_9O_5N$ requires C, 51·2; H, 4·3%). This was hydrogenated over palladium in acetic acid, yielding **2 : 3-*dihydro*-5-*methyl*-3-*oxobenz*-1 : 4-*oxazine*** as needles, m. p. 188—190° (from water) (Found : C, 66·5; H, 5·7. $C_9H_9O_2N$ requires C, 66·25; H, 5·6%). *N*-Methylation of this oxazine gave **2 : 3-*dihydro*-4 : 5-*dimethyl*-3-*oxobenz*-1 : 4-*oxazine*** as plates, m. p. 86—87° (from light petroleum, b. p. 60—80°) (Found : C, 67·7; H, 6·1. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3%).

β-*Chloropropion*-o-*anisidide*, m. p. 68° (from light petroleum, b. p. 40—60°), was prepared from *o*-anisidine and β-chloropropionyl chloride (Found : C, 56·3; H, 5·6; N, 6·4. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·7; N, 6·6%). When fused with aluminium chloride at 130° (10 min.) it afforded *o*-β-chloropropionamidophenol, m. p. 122—123° from benzene (charcoal) (Found : C, 54·1; H, 5·2; N, 7·2. Calc. for $C_9H_{10}O_2NCl$: C, 54·1; H, 5·05; N, 7·0%); Mayer *et al.* (*loc. cit.*) give m. p. 125°. A solution of this phenol in dilute aqueous sodium hydroxide was left for 2 hr. at room temperature, then acidified and extracted with ether. The recovered oil solidified when rubbed with benzene, affording ***o*-acrylamidophenol*** as leaflets, m. p. 122—123° (from benzene) (Found : C, 66·5; H, 5·85; N, 8·8; F, 1·04, by micro-hydrogenation in acetic acid over palladium. $C_9H_9O_2N$ requires C, 66·25; H, 5·7; N, 8·6%). Light absorption (in EtOH) $\lambda_{max.}$ 3000 Å (log ε, 3·9); (in NaOH) 2330, 3280 Å (log ε 4·6, 3·78); (in EtOH–NaOEt) 2400, 3000 Å (log ε 3·89, 3·82).

3 : 4-Dihydro-8-hydroxycarbostyril, m. p. 194° (Mayer *et al.*, *loc. cit.*, give m. p. 195°), was obtained by fusing **β-chloropropion-*o*-anisidide** (5 g.) with aluminium chloride (10 g.) at 220°

(1 hr.) (Found: C, 66·4; H, 5·7; N, 8·4. Calc. for $C_9H_9O_2N$: C, 66·2; H, 5·7; N, 8·6%). On methylation it afforded **3 : 4-*dihydro*-8-*methoxycarbostyril*** as irregular prisms, m. p. 97—98° (from light petroleum, b. p. 60—80°) (Found: C, 68·0; H, 6·4; N, 8·1. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%): light absorption (in EtOH): $\lambda_{max.}$ 2500, 2840 Å (log ε 4·00, 3·58). Reduction of this compound (0·6 g.) with lithium aluminium hydride (0·3 g.) in ether (50 c.c.) yielded, after 2 hr., 1 : 2 : 3 : 4-tetrahydro-8-methoxyquinoline which was identified as the benzoyl derivative, m. p. 132° undepressed by admixture with a specimen prepared by reduction of 8-methoxyquinoline (Tröger and Krückeberg, *J. pr. Chem.*, 1926, **114**, 249, give m. p. 136°).

3 : 4-*Dihydro*-8-*hydroxy*-1-*methylcarbostyril*.—To the oily β-chloro-*N*-methyl-*o*-propionanisidide (2 g.), prepared from *N*-methyl-*o*-anisidine and β-chloropropionyl chloride, anhydrous aluminium chloride (4 g.) was added, and the mixture heated at 110° for 1 hr. After recovery, **3 : 4-*dihydro*-8-*hydroxy*-1-*methylcarbostyril*** was obtained as needles, m. p. 195—196° (from benzene) (Found: C, 68·0; H, 6·55; N, 7·8. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). Light absorption (in EtOH): $\lambda_{max.}$ 2490, 2890 Å (log ε 3·96, 3·67). On methylation the compound formed **3 : 4-*dihydro*-8-*methoxy*-1-*methylcarbostyril***, m. p. 86° (from light petroleum, b. p. 40—60°) (Found: C, 69·15; H, 6·8; N, 7·4. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%): light absorption (in EtOH): $\lambda_{max.}$ 2510, 2900 Å (log ε 4·07, 3·73). Reduction of this compound (0·5 g.) with lithium aluminium hydride (0·3 g.) in ether (75 c.c.) yielded, after 5 hr., 1 : 2 : 3 : 4-tetrahydro-8-methoxy-1-methylquinoline, identified as its chloroplatinate, m. p. 198° (decomp.) from water [Fischer and Köhn, *Ber.*, 1886, **19**, 1040, give m. p. 199° (decomp.)].

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The Infrared Spectra of Coals.

By J. K. BROWN.

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The infrared spectra from 650 to 4000 cm.$^{-1}$ for twelve vitrains are presented and their variations with carbon content are discussed. A similar basic skeleton for coals over a wide range of carbon content is indicated by the general similarity of the spectra, but two well-defined changes in the absorption bands assigned to substituent groups have been observed. One indicates a decrease in the number of hydrogen-bonded OH groups with increase in carbon content; this is virtually complete in the region of 89% of carbon, and is accompanied by an increase in aromatic hydrogen. The other is a reduction in the aliphatic material with increase in carbon content which is most marked between 90 and 94% of carbon. This is accompanied by an increase of structureless absorption in the spectra which is tentatively interpreted as due to an electronic absorption of condensed aromatic rings. A semiquantitative measure of the ratio of CH (aliphatic)/CH (aromatic) links is made. The possibility of aromatic ether or quinone structures is discussed with particular reference to the 1600-cm.$^{-1}$ absorption band. The region between 900 and 700 cm.$^{-1}$ is analysed in terms of the pattern of aromatic hydrogen atoms.

FEW infrared spectra of coals have been published, but several papers deal with the spectra of thin sections of coal (Cannon and Sutherland, *Trans. Faraday Soc.*, 1945, **41**, 279; Friedel and Pelipetz, *J. Opt. Soc. Amer.*, 1953, **43**, 11), of coal as powder suspensions in Nujol (Cannon and Sutherland, *Nature*, 1945, **156**, 240; Gordon, Adams, and Jenkins, *ibid.*, 1952, **170**, 317; Cannon, *ibid.*, 1953, **171**, 308), and of various solvent extracts and reaction products (Cannon and Sutherland, *Trans. Faraday Soc.*, 1945, **41**, 279). This paper describes the spectra of a series of coals covering a wide range of carbon content; comparison of these spectra allows an analysis to be made in terms of chemical structure,

so that the relation between structures present in different coals can be established, and information about the chemical changes accompanying coalification can be derived. Some work on these lines has already been carried out by Cannon (*loc. cit.*). Although the spectrum of a thin section of coal shows all the absorption bands without interference, the Nujol mull method is more convenient for the study of a wide range of coals and coal products, and this technique has been used in the present work.

Experimental

All coals consist of a number of components which are distinguished mainly by their appearance under the microscope though partly by their chemical composition. Of these constituents vitrain is the most abundant and homogeneous; the materials used in the present investigation were all vitrains picked out by hand from the seams listed in Table 1 (where the analyses given are those of the vitrains, not of the whole coal).

The coals were examined as mulls in the spectral region 650—2000 cm.$^{-1}$ in Nujol and in the region 2000—4000 cm.$^{-1}$ in hexachlorobutadiene. The lump coals were powdered and dried in a vacuum-desiccator for 24 hr. They were transferred to the mulling agent in an agate mortar and ground for 8 hr.; longer periods of grinding did not reduce the scattering of the radiation significantly. About equal weights of powdered coal and mulling agent were used for each coal, though for the hexachlorobutadiene mulls the liquid tended to evaporate slowly during grinding and more had to be added from time to time to maintain a smooth paste. Finally, the paste was spread in the usual manner between rock-salt plates separated by a fixed spacer.

Table 1. *Analyses of vitrains.*

Source	Per cent. by wt. of dry, mineral-matter-free coal					Per cent. by wt. of coal analysed		Loss in wt. on heating to 925°: % of dry ash-free coal †
	C	H	N	S	O (by diff.)	Moisture *	Ash	
Leicestershire, Eureka Seam	78·3	5·2	1·6	0·7	14·2	12·4	1·0	42·2
Staffordshire, Cannock Wood Shallow Seam	80·4	5·3	1·7	0·9	12·0	13·0	0·7	43·1
Northumberland, Ellington High Main	81·8	5·3	1·8	—	11·1	9·6	0·9	37·4
N.E. Division, Steetley Unit Clowne Seam	83·2	5·6	2·0	0·7	8·5	8·0	1·2	—
Orgreave Colliery (Yorks), Flockton Brights (coking coal ‡)	85·4	5·3	1·6	1·0	6·6	2·7	0·9	35·2
N.E. Division, Grimethorpe Unit, Parkgate Seam (coking coal ‡)	87·3	5·4	1·8	0·9	4·6	1·8	0·7	—
S.W. Division, Coedley, Pentre Seam (coking coal ‡)	88·7	5·1	1·4	0·6	4·2	1·0	1·7	30·2
Durham Division, Langley Park, Victoria Seam (coking coal ‡)	89·3	5·1	1·8	0·9	2·9	1·1	0·2	26·4
S.W. Division, Coegnant, Gellideg Seam (steam coal ‡)	91·4	4·4	1·4	0·8	2·0	0·7	1·1	15·9
S.W. Division, Fforchaman, Gellideg Seam (steam coal ‡)	92·8	3·9	—	—	—	1·0	1·2	9·8
S.W. Division, Llandebie Middle Seam (anthracite ‡)	94·1	3·1	—	—	—	2·4	0·7	5·3
S.W. Division, Pontyberem, Lower Pumpquart Seam (anthracite ‡)	94·1	3·0	0·9	—	1·4	1·4	1·2	5·3

* Loss in wt. at 105—110° in 1½ hr. *in vacuo*.

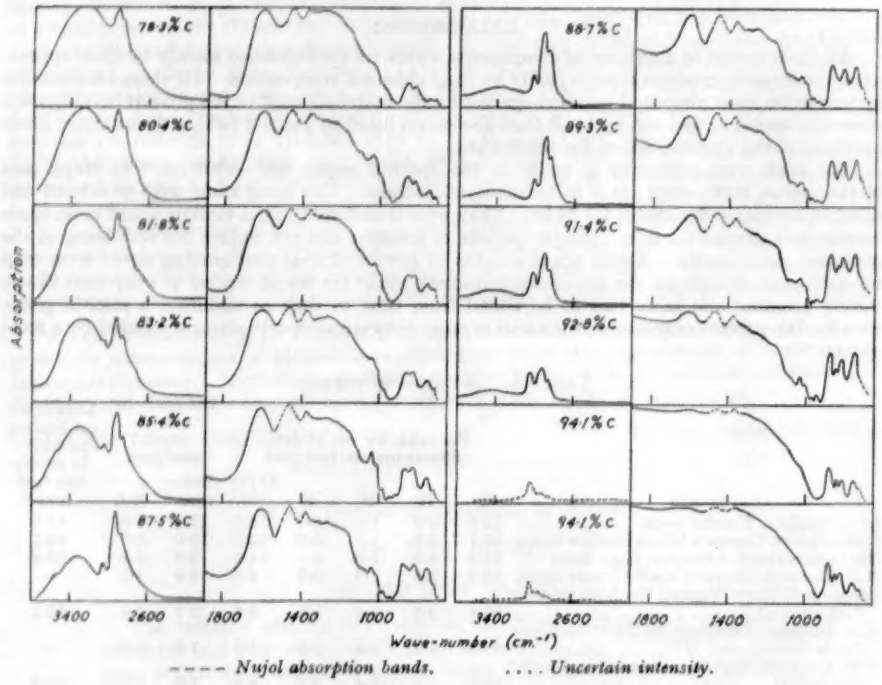
† Under conditions specified for "Volatile Matter" test in B.S.S. No. 1016; results corrected for CO_2 (data included as additional means of identifying the material used).

‡ These descriptions of the vitrains are used in the Discussion and are included here for reference. For the relation of these to coal classification, see Moffatt, Hicks, and Matthews, *Combustion Engineering*, 1950, 150.

A Hilger D209 double-beam spectrometer was used, with a 30° rock-salt prism for the region 650—2000 cm.$^{-1}$ and a 30° fluorite prism for the region 2000—4000 cm.$^{-1}$. No allowance was made for any change in the level of background absorption with wave-length in the region 650—2000 cm.$^{-1}$; the signal in the blank beam of the spectrometer was adjusted so that at the beginning of the run (near 700 cm.$^{-1}$) the trace was close to the 100% transmission line. The only alteration made after this adjustment was in the slit width, which was periodically reduced throughout the region. For the region 2000—4000 cm.$^{-1}$ the instrument was again set so that at the beginning of the run (near 2000 cm.$^{-1}$) transmission was near the 100% line, and the

spectrum was examined as before without any scattering material in the blank beam. In measuring the spectra obtained for this region, a background curve was drawn in; this coincided with the recorder trace outside the region of discrete absorption bands. In this way a quantitative estimate of each of the absorption bands was possible. The spectra of the range of vitrains are shown in Fig. 1.

FIG. 1. *Infrared spectra of a range of vitrains between* 650 *and* 4000 *cm.*$^{-1}$.



---- *Nujol absorption bands.* .... *Uncertain intensity.*

DISCUSSION

Assignment of Vibration Frequencies to Substituent Groups.—The spectrum of the Flockton coal (85·4% of carbon) can be taken as representative of the series, as it shows most of the frequencies observed in coal spectra; these are listed in Table 2 together with the assignments proposed. Since it is difficult to distinguish between the vibration frequencies of aliphatic chains and alicyclic or hydroaromatic systems in complex structures, the term aliphatic group will be used to include all these types.

The small amount (<2%) of nitrogen present in the coals makes it certain that the broad absorption band near 3300 cm.$^{-1}$ arises principally from hydrogen-bonded OH groups; the strong absorption near 1250 cm.$^{-1}$ suggests that these are mainly phenolic (cf. Cannon, *loc. cit.*). Adsorbed water can also give rise to a band near 3300 cm.$^{-1}$, but since heating a coal to 105° for one day under a high vacuum did not significantly reduce the intensity of the OH absorption band, this explanation seems unlikely. The frequencies near 3000 cm.$^{-1}$ indicate the presence of aromatic CH and aliphatic groups; the latter should give rise to the well-known frequencies at 1460 and 1380 cm.$^{-1}$, but in the spectra shown in Fig. 1 they are masked by the strong absorption bands of Nujol. These absorption bands have been detected in thin sections of coal and in coal extracts (Cannon and Sutherland, *Trans. Faraday Soc.*, 1945, **41**, 279; Friedel and Pelipetz, *loc. cit.*; Hadzi, *Acad. Sci. and Art, Sloven.*, Class III, Ser. A, 1951, **3**, 99; Brown, unpublished work). Absorption bands near 1460 cm.$^{-1}$ may also be assigned to aromatic ring frequencies.

The above conclusions are similar to those given by Cannon (*loc. cit.*) except that he observed absorption bands at 1730 and 1690 cm.$^{-1}$ (assigned to ester groups and aldehyde or keto-groups, respectively) which have not been detected in the vitrain spectra. They have, however, been found in a spore-rich durain (Brown, unpublished work), so it is possible

TABLE 2. *Assignment of frequencies observed in coal spectra.*

Frequency (cm.$^{-1}$)	Assignment
ca. 3500 (w)	Hydrogen-bonded OH/NH
ca. 3300 (s)	Hydrogen-bonded OH/NH
3030 (w)	Aromatic C–H stretching
2920, 2850 (s)	Aliphatic CH_2 and CH_3 stretching
ca. 1605 (s)	Aromatic ring frequency *
1160—1300 (s)	C–O stretching of phenols, aromatic ethers. OH deformation. Quinones
1060—1160 (m)	C–O stretching of alcohols, linear and cyclic ethers
ca. 1030 (m)	C–O stretching of aromatic ethers of the type Ph·O·CH_2R
860, 820, 750 (w)	Aromatic C–H out-of-plane vibration frequencies observed in a number of single and condensed ring structures

* See discussion (p. 751). (s) = strong; (m) = medium; (w) = weak.

that the absorption bands arose from spore material in the bright coals investigated by Cannon.

Changes in Spectra with Carbon Content.—(a) *The background.* The general background level of absorption in the infra-red spectra of coals has been shown to vary with carbon content (Cannon, *loc. cit.*). In the spectra studied in this work the level between 78 and 88% of carbon remains roughly constant. For higher carbon contents there is a marked increase which becomes very pronounced in the steam coals and anthracites. The background level increases with decrease in wave-length and is most clearly seen at the short wave-length end of the Nujol mull spectra (*i.e.*, 2000 cm.$^{-1}$). The effect is not illustrated in the region 2000—4000 cm.$^{-1}$, as here the background trace was taken as coincident with the 100% transmission line.

The effect could be explained as an apparent absorption, which arises from the scattering of radiation by the powdered coal. This explanation seems unlikely, since microscopic examination showed that the average particle size in the mulls of coals with carbon contents between 89 and 94% did not differ significantly from those of coals with lower percentages of carbon. Further, although the refractive index of vitrains increases with carbon content (Cannon and George, Proc. Conf. Ultrafine Structure of Coals and Cokes, B.C.U.R.A., London, 1944, 290; van Krevelen, *Brennstoff-Chem.*, 1953, **34**, 167) the change cannot be closely correlated with the variation in background absorption. The change does, however, follow the development of marked optical anisotropy (Cannon and George, *loc. cit.*) and the growth of graphitic crystallites established by *X*-ray studies (Riley *et al.*, Proc. Conf. etc., 176). The reflectance and absorption coefficient of vitrains in the visible region also increase markedly in the range 89—94% of carbon (Seyler, *ibid.*, p. 270; Cannon and George, *ibid.*, p. 290; van Krevelen, *loc. cit.*). The structureless absorption in the infra-red region can be explained, following Cannon (*loc. cit.*), as arising from the transition of an aromatic structure to a graphite-type lattice. The observation that a dispersion of graphite in Nujol of 2-μ thickness shows a continuous structureless absorption of 70—80% over the whole range 5000—650 cm.$^{-1}$ (Cannon, *loc. cit.*) supports this view. Further, Kmetko (*Phys. Review*, 1951, **82**, 456) has found that in the infra-red spectra of Cellophane chars an "absorption" edge moves across the region 5000—650 cm.$^{-1}$ from the visible with increasing temperature of carbonisation. He attributes this effect to the motion of electrons in a graphite-type lattice and discusses it in terms of semi-conductor properties. Work on the electrical conductivity of polycyclic aromatic compounds (Inokuchi, *Bull. Chem. Soc. Japan*, 1951, **24**, 222) has been interpreted in a similar manner; the energy difference between the empty and the occupied levels in these semiconductors decreases with increasing number of π-electrons in the molecule. This number is directly related to the number of condensed rings. Ultimately the energy difference is sufficiently small for electronic transitions to lie in the infra-red region. It is therefore reasonable to attribute the absorption edge observed in the coal spectra to the presence of condensed-ring structures which

increase markedly in size at carbon contents higher than approximately 89%. Even in the anthracite spectra the absorption edge lies well within the range 4000—650 cm.$^{-1}$, which suggests that the structures in these coals are somewhere between an assembly of large polynuclear hydrocarbons and graphite.

The spectrum of an anthracite published by Gordon, Adams, and Jenkins (*loc. cit.*) differs from those shown in Fig. 1 in that the increase in background absorption with decreasing wave-length is not shown. Presumably these authors have considered the effect to arise from the scattering of radiation and have consequently measured their curves from standard backgrounds obtained by suspensions of spectroscopic carbon in Nujol.

(b) *Variation of oxygen groupings with carbon content.* Fig. 1 shows that, as expected, the intensity of absorption bands assigned to oxygen-containing groups decreases with the oxygen content of the vitrain. The hydrogen-bonded OH absorption band near 3300 cm.$^{-1}$ shows the most marked effect. For the carbon content range 78—84% this band is strong and overlaps the C–H stretching absorption bands near 3000 cm.$^{-1}$; as the carbon content increases it becomes progressively less prominent, and in vitrains with more than 89% of carbon it is very weak. This change can be correlated with a change in the pattern of absorption between 900 and 700 cm.$^{-1}$. The decrease in intensity of the OH band also correlates well with the extractability of coals by solvents such as ethylenediamine (Dryden, *Fuel*, 1951, **30**, 217).

The broad region of absorption between 1300 and 1160 cm.$^{-1}$ also decreases in intensity with carbon content in accordance with the assignment given in Table 1. However, marked absorption remains in this region even when the hydrogen-bonded OH band at 3300 cm.$^{-1}$ is weak; this residual absorption may arise from aromatic ether linkages.

(c) *The aliphatic and aromatic hydrogen.* The variation in the proportions of aliphatic and aromatic CH groups in the structure with increase in carbon content can readily be followed from the intensities of the absorption bands that arise from their stretching vibrations at 2850, 2920, and 3030 cm.$^{-1}$. Fig. 1 shows that the aliphatic C–H stretching absorption bands are strong over a considerable range of carbon content; there is a decrease in intensity with increase in the percentage of carbon which is particularly marked in the range 90—94% of carbon. The aromatic C–H stretching absorption band increases in intensity as far as the beginning of the anthracite region (93% carbon); at 94% of carbon, qualitative estimates indicate that there is a decrease in intensity.

In order to compare quantitatively the relative intensities of the aromatic and aliphatic C–H stretching absorption bands for coals of different carbon contents, the optical densities for the 3030 cm.$^{-1}$ absorption band, $D_{ar.}$, and for the 2920 cm.$^{-1}$ absorption band, $D_{al.}$, were measured; D, the optical density, is defined by $D = \log_{10} I_0/I$, where I_0 is the intensity of the incident radiation and I that transmitted by the sample. To estimate the optical densities, a background was drawn in as accurately as possible and allowance was made for the overlapping wings of the two absorption bands. No attempt was made to correct for the presence of the 2850-cm.$^{-1}$ absorption band, as the method was only used empirically. The strength of the hydrogen-bonded OH band in the coals with carbon contents between 78 and 84% prevented quantitative estimate of $D_{ar.}/D_{al.}$. A rough measure was possible for coals with carbon contents near 84%; at higher percentages of carbon the accuracy was improved since the OH absorption band intensity was much reduced. At 94% of carbon, measurement was again difficult owing to the high background absorption. A large number of runs were made for each coal and the average of the results taken. The values of $D_{ar.}/D_{al.}$ are plotted against the percentage of carbon in Fig. 2. Several coals not listed in Table 1 are included; these fit on to the curve very satisfactorily. It is clear that there is a marked increase in the ratio of $D_{ar.}/D_{al.}$ with increase in carbon content; this is most pronounced in the region 90—94% of carbon.

The optical densities, $D_{ar.}$ and $D_{al.}$, are related to the extinction coefficients per C–H bond, $\varepsilon_{ar.}$ and $\varepsilon_{al.}$, and to the number of bonds of each type, $n_{ar.}$ and $n_{al.}$, by $D_{ar.}/D_{al.} = (\varepsilon_{ar.}/\varepsilon_{al.})(n_{ar.}/n_{al.})$.

The exact nature of the chemical structures present in coal is unknown, so that values of $\varepsilon_{ar.}/\varepsilon_{al.}$ must be obtained indirectly in order to estimate $n_{ar.}/n_{al.}$. Aromatic molecules certainly occur which, it will be assumed, have aliphatic chains attached to them or contain

alicyclic rings. A number of reference compounds of this type (with 3—5 condensed rings) were examined as mulls in hexachlorobutadiene. From the measurements of $D_{ar.}/D_{al.}$ and the known values of $n_{ar.}/n_{al.}$ in these compounds the values of $\varepsilon_{ar.}/\varepsilon_{al.}$ were found to vary between 0·3 and 1·0. A value of 0·5 has been taken for the coals, so that an order of magnitude of $n_{ar.}/n_{al.}$ can be deduced from Fig. 2. At 92% of carbon, where $D_{ar.}/D_{al.}$ is approximately 0·5, there is roughly one aromatic C–H bond for each aliphatic C–H bond in the structure; at 84% of carbon the ratio of $n_{ar.}/n_{al.}$ is approximately 0·25.

(d) *Variation in aromatic substitution with carbon content.* The pattern of absorption bands between 900 and 700 cm.$^{-1}$ (which arises from the out-of-plane vibration of aromatic CH bonds) can be used to follow the changes in aromatic substitution with carbon content. Fig. 1 shows that, as the carbon content of the vitrain increases, the absorption bands in the above region also increase in intensity. Three main absorption peaks are observed in the spectra; at the beginning of the range they lie at approximately 860, 825, and 750 cm.$^{-1}$. The 750-cm.$^{-1}$ absorption band is markedly weaker than the others. With increase in carbon content there is a gradual shift in the position of the 860 and 825 cm.$^{-1}$ absorption bands; in coals with carbon contents above 90% they reach positions near 874 and 814 cm.$^{-1}$, respectively. The 750-cm.$^{-1}$ absorption band increases in intensity relative to the others as the percentage of carbon increases until, in coals with carbon contents near 89%,

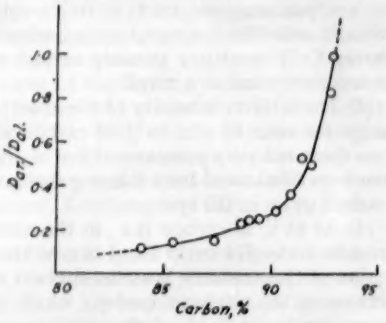


FIG. 2. *Ratio of the optical density of the* 3030-*cm.*$^{-1}$ *and* 2920-*cm.*$^{-1}$ *absorption bands, plotted against carbon content for a range of vitrains.*

it has a strength approximately equal to that of the two higher-frequency absorption bands. In the spectra of coals with percentages of carbon between 90 and 93% the pattern remains almost unchanged although there is an overall increase in intensity; a weaker, but nevertheless clearly defined, absorption band appears in this range at 840 cm.$^{-1}$. In the anthracites (94% of carbon) there is a change in the pattern; the 750-cm.$^{-1}$ and 814-cm.$^{-1}$ absorption bands decrease in intensity and the 874-cm.$^{-1}$ absorption band becomes the strongest in the region 700—900 cm.$^{-1}$. The pattern observed for the anthracites is different from that shown in the spectrum published by Gordon, Adams, and Jenkins (*loc. cit.*), where only one absorption band, near 720 cm.$^{-1}$, has been recorded.

Strong absorption bands in the region 700—900 cm.$^{-1}$ are present in the spectra of many single- and condensed-ring aromatic structures. These bands have mainly been assigned to out-of-plane C–H vibrations. Correlations between the type of substitution and the aromatic C–H out-of-plane vibration frequencies have been derived for a number of substituted benzenes and are now well established (*e.g.*, see McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318; Gourlay, *Research*, 1950, **3**, 342). A discussion of these in terms of the number of adjacent hydrogen atoms on the ring (Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 64) shows that, as this number is reduced by substitution, the frequency of out-of-plane motion increases from a value near 750 cm.$^{-1}$ when five C–H bonds are present to approximately 870 cm.$^{-1}$ when one remains. The trend is also observed in the spectra of condensed aromatic hydrocarbons. Several authors (Cannon and Sutherland, *Spectrochim. Acta*, 1951, **4**, 373; Orr and Thompson, *J.*, 1950, 218; Dannenburg, Schiedt, and Steidle, *Z. Naturforsch.*, 1953, **8**, *b*, 269) have been able to

correlate regions of absorption in the range 900—700 cm.$^{-1}$ in the spectra of a number of linear and angular condensed aromatic systems by considering each ring in terms of its substituted benzene analogue; in such cases each condensed ring substitutes two positions on its neighbour. The correlations between number of neighbouring aromatic hydrogen atoms on each ring and the observed out-of-plane frequencies lead to similar conclusions but have the advantage that substitution in the coal structure can be discussed without detailed consideration of the ring configurations. If single aromatic nuclei are present in the coal structure the absence of strong absorption near 690 and 770 cm.$^{-1}$ means that the concentration of mono-, *meta*-, 1 : 2 : 3-, and 1 : 3 : 5-substituted rings must be small. The main conclusions concerning the degree of aromatic substitution are as follows:

(1) The presence of absorption near 860 cm.$^{-1}$ in coals at the lower end of the range of carbon contents, taken in conjunction with the fact that the 750-cm.$^{-1}$ absorption band is relatively weak, suggests that aromatic systems containing isolated C–H bonds are important, *i.e.*, the degree of substitution is high. This agrees with the observation that the aliphatic C–H and hydrogen-bonded OH absorption bands are strong in these coals.

(2) The marked increase in intensity of the absorption band at 750 cm.$^{-1}$ with increase in carbon content shows that the degree of substitution of part of the system is reduced. This change correlates well with the decrease in intensity of the OH absorption band, which appears only weakly in the spectra of coals with carbon contents of 89% and above. The analysis suggests that, if single ring systems are present, decrease in substitution produces *ortho*-disubstituted nuclei, whereas for condensed systems end rings (four neighbouring C–H bonds) or possibly certain corner rings (three neighbouring C–H bonds) are left unsubstituted as a result.

(3) The relative intensity of the absorption bands in the region 900—700 cm.$^{-1}$ does not change between 89 and 93% of carbon although there is an overall increase in intensity. Since there is a very pronounced loss of aliphatic groups in the above range, these groupings have been eliminated from the ring systems without affecting materially the overall balance of substitution in the system.

(4) At 94% of carbon (*i.e.*, in the anthracites) the overall degree of substitution again increases; the 874-cm.$^{-1}$ band is now the most prominent. This means that a large proportion of the aromatic systems contain isolated C–H bonds in spite of the further marked decrease in the aliphatic content which has taken place. Further, the intensity of some absorption bands in the anthracite spectra has decreased, which suggests that the amount of aromatic hydrogen on the rings in these coals is less than in those of 93% carbon content.

Further deductions can be made from the observations. The spectra show that a well-marked absorption band occurs near 870 cm.$^{-1}$ for all the coals; this implies that the degree of substitution of part of the system remains high throughout the range. In terms of isolated ring structures it indicates pentasubstitution which, in the anthracites, predominates over all other types. Such a high degree of substitution is not readily maintained because in the range 90—94% of carbon the aliphatic material is almost entirely eliminated. In a system containing condensed aromatic structures this difficulty does not arise, for a high degree of substitution can be maintained by neighbouring rings in the structure. The predominance of isolated C–H bonds in the anthracite structure is then readily explained in terms of large condensed aromatic systems, which would contain a considerable number of such bonds on their periphery. The process by which coking coals (89% of carbon) are converted into semi-anthracites (93% of carbon) is pictured as one in which the degree of condensation of the aromatic structures is increased by ring closure or by cross-linking with the elimination of aliphatic groups. The formation of the anthracites studied in the present work has entailed a loss not only of aliphatic but also of aromatic hydrogen; the interpretation given earlier suggests that some of this loss of aromatic hydrogen has taken place from end or corner rings of the condensed systems (correlated with the 750-cm.$^{-1}$ band). A possible mechanism would be one in which condensed ring structures, built up in the way already suggested, cluster together to form large polycyclic systems. The growth of the condensed units in coal structure in the range 90—94% of carbon is entirely consistent with the interpretation of the increase in background absorption observed in the above region.

(e) *The 1600-cm.$^{-1}$ absorption band.* Absorption bands near 1600 cm.$^{-1}$ occur in a wide range of single- and condensed-ring aromatic compounds; they arise from ring vibrations. The intensity of these bands is very variable but, with few exceptions, it is not great in the alkyl-substituted benzenes * and is generally weak in condensed aromatic hydrocarbons which contain more than three rings (Cannon and Sutherland, *Spectrochim. Acta, loc. cit.*). A very pronounced absorption band near 1600 cm.$^{-1}$ is present in the spectra of all the coals, except in the anthracites, where the high background absorption obliterates the spectra in this region. It is probable that the aromatic ring vibration bands are enhanced in intensity by a polar grouping attached to the aromatic systems, or the polar grouping itself may have a vibration frequency near to 1600 cm.$^{-1}$. Phenolic OH groups are not mainly responsible for the effect, as there is no marked diminution in intensity of the band with increase in carbon content. Aromatic ether linkages are one possibility. Very few reference compounds are available to test this hypothesis; diphenyl ether has a strong absorption band near 1600 cm.$^{-1}$ (Barnes, Gore, Liddel, and Williams, " Infra-red Spectroscopy," Reinhold Publ. Corp., New York, 1944, p. 70) and so also do lignins (*e.g.*, see Schubert and Nord, *J. Amer. Chem. Soc.*, 1950, **72**, 3835). Diphenylene oxide, which contains oxygen in a five-membered ring, does not show the effect (Barnes *et al.*, *loc. cit.*). Another possibility is that the absorption band arises from a carbonyl group which forms part of the aromatic system. Polycyclic extended quinones which have hydroxyl groups in the *peri*-position to the carbonyl groups can have carbonyl frequencies close to 1600 cm.$^{-1}$; *e.g.*, hipericin, 1589 cm.$^{-1}$, and 4 : 4′-dihydroxyhelianthrone, 1607 cm.$^{-1}$. The strong internal hydrogen-bonding which, in part, is the cause of the very low carbonyl frequency also causes a marked shift and weakening of the hydroxyl absorption bands. Where such absorption bands have been detected in chelated six-membered ring systems they have been found to be centred in the region 2700—3000 cm.$^{-1}$. In the spectra of coals containing strong OH absorption bands these do indeed extend to the low-frequency side of the C–H stretching fundamentals. Other systems which give carbonyl frequencies close to 1600 cm.$^{-1}$ have been discussed by Hunsberger, Ketcham, and Gutowsky (*J. Amer. Chem. Soc.*, 1952, **74**, 4839).

It is not possible to distinguish further between the two types of structure which have been discussed above. A correct interpretation of the reasons for a pronounced 1600-cm.$^{-1}$ absorption band in coal spectra is important; the band has been observed in the spectra of coals carbonised at 500° (Brown, following paper, p. 756) and also in all the coal extracts which have so far been examined (Cannon and Sutherland, *Trans. Faraday Soc.*, 1945, **41**, 279; Hadzi, *loc. cit.*; Brown, unpublished work). A strong absorption band in the above position has also been found in the spectra of sugar and Cellophane chars (Friedel and Pelipetz, *loc. cit.*).

Conclusion.—The preceding discussion has shown that the infra-red spectra provide valuable information concerning the nature and variation with carbon content of the substituent groups in coal structure, as well as some indirect conclusions about the nature of the aromatic systems. Two well-defined changes have been detected; the first is the loss of hydrogen-bonded OH groups (probably mainly phenolic) which is near completion in coals containing 89% of carbon. In the range of carbon contents 78—89% there is a marked decrease in the oxygen to carbon ratios (78% C, O/C = 0·14; 89% C, O/C = 0·03) which, as expected, accompanies this change. It may be significant that coals near the upper limit of this range (89% of carbon) show the strongest coking properties, and further, that they have the lowest viscosity (van Krevelen, *loc. cit.*) and porosity (King and Wilkins, Proc. Conf. etc., *loc. cit.*, p. 46; Franklin, *Trans. Faraday Soc.*, 1949, **45**, 274). The second change, which is most marked between 89 and 94% of carbon, is a decrease in the amount of aliphatic material. There is a corresponding reduction in the H/C ratios (89% C, H/C = 0·7; 94% C, H/C = 0·4). The infra-red data for this range of carbon content suggest that condensed aromatic structures occur and the removal of aliphatic material promotes their growth.

Finally, the coals selected for study have, in a number of cases, been obtained from

* In these compounds the 1600-cm.$^{-1}$ absorption band is accompanied by a stronger one near 1500 cm.$^{-1}$; this is not evident in the coal spectra.

sources which are geographically widely separated. As the changes which have been followed occur continuously throughout the series, it appears that these aspects of the process of vitrinisation are of general applicability. Other modifications of coal spectra which are produced by carbonisation and solvent extraction will be discussed in further papers. Throughout the discussion in preceding sections it has been tacitly assumed that the aromatic and non-aromatic materials form part of a single system. It has not been possible, so far, to separate vitrains into widely different materials, and therefore the above assumption is reasonable.

Note added, January 31st, 1955.—Gordon *et al.* (*Nature*, 1954, **174** 1098) have shown recently that a large reduction of the background present in spectra of coals of high carbon content in Nujol mulls can be achieved by prolonged ball-mill grinding of the samples with potassium bromide and subsequent pressing to a disc. This strongly suggests that the effect arises from the scattering of radiation.

This work forms part of researches on the chemical constitution of coal carried out in the laboratories of the British Coal Utilisation Research Association, and is published by permission of the Director General. The author is indebted to Dr. I. G. C. Dryden for his assistance in formulating the terms of the research problem, to Dr. N. Sheppard for his advice and continued interest, and to Dr. P. B. Hirsch, of the Cavendish Laboratory, Cambridge, for most stimulating discussions. The work was carried out in the Department of Colloid Science, Cambridge, by kind permission of Professor F. J. W. Roughton, F.R.S.

British Coal Utilisation Research Association,
Randalls Road, Leatherhead, Surrey. [*Received, July 16th,* 1954.]

Infrared Studies of Carbonised Coals.

By J. K. Brown.

[Reprint Order No. 5563.]

A weakly caking and a strongly coking coal, carbonised at temperatures up to 800°, have been examined by infrared methods. The most marked changes in the spectra are caused by heating to between 400° and 550°; they indicate a loss of aliphatic CH and phenolic OH groups. It is suggested that the different physical changes which occur in the two coals at temperatures between 400° and 460° result, in part, from the presence of phenolic material in the caking coal and its absence in the coking coal. A pyrolysis mechanism is proposed in which aliphatic groups are replaced mainly by C–C bonds between the aromatic systems; this begins in the temperature range 400—550°. The process is continued at higher temperatures with the loss of aromatic hydrogen, and some graphitisation ensues.

In the preceding paper the infra-red spectra of a range of vitrains were discussed. The present paper describes infra-red studies of heated coals. Infra-red methods have not been applied previously to the study of coal carbonisation although the spectra of several products have been published. They include the spectra of a " shock-heater " distillate (Cannon and Sutherland, *Trans. Faraday Soc.*, **1945**, **41**, 279), a pitch (Gordon, Adams, and Jenkins, *Nature*, **1952**, **170**, 317), and two pitch extracts (Cannon and Sutherland, *loc. cit.*).

Two coals have been studied in the present work, *viz.*, a " caking " and a " coking " coal. Briefly, a caking coal, when heated to 350—400°, first softens and contracts, and on further heating the particles sinter together and a slight swelling occurs; the shape of the product is similar to that of the unheated specimen. A coking coal, heated in the same temperature range, becomes semi-fluid (near 400°) and contracts slightly; then, at temperatures between 400° and 450°, it swells markedly and at higher temperatures the plastic mass, inflated by the gases evolved in its decomposition, sets to a solid with a highly developed bubble structure. In both cases the product is termed a semi-coke. Heating to temperatures beyond 550° transforms the semi-coke into a more compacted coke structure.

Little is known concerning the chemical changes which occur when coals are heated. Analyses show that the H/C and O/C ratios decrease with increasing temperature of carbonisation (see, *e.g.*, van Krevelen, *Fuel*, 1950, **29**, 269). The structure of the residual coal after carbonisation has been studied by *X*-ray methods (Blayden, Gibson, and Riley, Proc. Conf. Ultrafine Structure of Coals and Cokes, B.C.U.R.A., London, 1944, p. 342; Franklin, *Proc. Roy. Soc.*, 1951, **209**, *A*, 196); the process has been discussed in terms of a turbostratic system of graphitic crystallites in which the lamellæ change in size and degree of order.

The two coals studied in this work were carbonised at various temperatures up to 800°.

Experimental

The weakly caking coal selected was a Northumberland vitrain; its chemical composition on a dry mineral-matter-free basis (Parr formula) was C, 81·8; H, 5·3; N, 1·8; O (by diff.), 11·1%. Corresponding values for the Durham coking coal were 88·8, 5·1, 1·6, and 4·5%. Each was ground to −72 B.S.S. and heated in nitrogen at the rate of 1½°/min. to temperatures of 300°, 400°, 460°, 550°, and 800°; they were kept at these temperatures for 1 hr. The method of preparation of the samples for infra-red examination, the instrument used in recording the spectra, and the procedure employed in drawing the background, were as described in the preceding paper. The spectra of the Northumberland coal are shown in Figs. 1*a* to 1*e*, and those of the Durham coking coal in Figs. 2*a* to 2*e*.

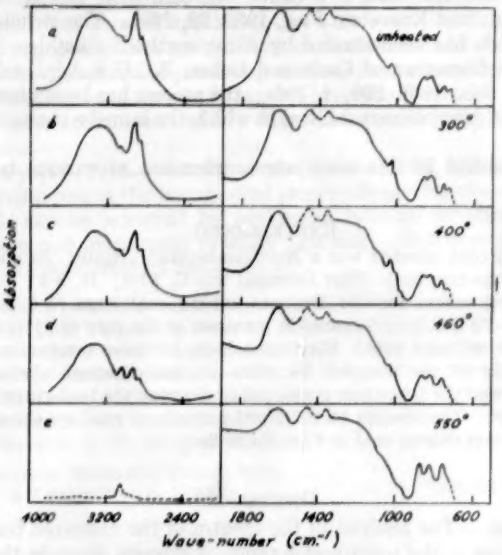
Discussion

(a) *Unheated Coals.*—The analysis of the spectra of the unheated coals follows directly from the interpretation of the spectra of a range of vitrains given in the preceding paper. The most significant features in the spectrum of the Northumberland coal are strong absorption bands arising from hydrogen-bonded OH (near 3300 cm.$^{-1}$) and aliphatic (or alicyclic) CH groups (2920 and 2850 cm.$^{-1}$). Much weaker absorption bands, arising from the out-of-plane motion of aromatic CH bonds, are observed near 750, 820, and 860 cm.$^{-1}$, *i.e.*, in the positions previously found for other coals with similar carbon content (82%). The spectrum of the unheated coking coal (Fig. 2*a*) shows all the characteristics of a vitrain of carbon content near 89%, *viz.*, a weak hydrogen-bonded OH absorption band, and a ratio of the optical densities of aromatic CH to aliphatic CH stretching absorption bands, $D_{ar.}/D_{al.}$, of approx. 0·25. The out-of-plane aromatic CH bands lie at 750, 814, and 870 cm.$^{-1}$. The spectrum of the coking coal shows a well-defined background absorption which, from previous work (Cannon, *Nature*, 1953, **171**, 308; Brown, *loc. cit.*), has been tentatively ascribed to an electronic effect associated with polycyclic aromatic structures. A very pronounced absorption band at approx. 1030 cm.$^{-1}$ in the spectrum of the coking coal may be associated with inorganic material (the ash content was 2·6%).

(b) *Coals heated at 300° and 400°.*—There is very little change in the spectra of the coals heated to 300° and 400°. The hydrogen-bonded OH absorption band in the spectrum of the unheated caking coal (Fig. 1*a*) has decreased in intensity, but is still very pronounced. The decrease may have been a result of the removal of absorbed water or some other hydroxylic material, or it may have been due to a chemical change, *e.g.*, formation of ether linkages from phenolic structures. No change is observed in the intensities or positions of the aromatic CH absorption bands between 900 and 700 cm.$^{-1}$. The spectra of both coals at 300° and 400° show a decrease in the intensity of the aliphatic (or alicyclic) CH stretching absorption bands. The decrease could not be estimated for the Northumberland coal owing to the overlapping OH absorption band; however, the reduction in intensity is not marked. A quantitative estimate of the ratio $D_{ar.}/D_{al.}$ was made for the Durham coking coal; at 300° the value is 0·27 and at 400° 0·33, compared with 0·25 for the unheated sample.

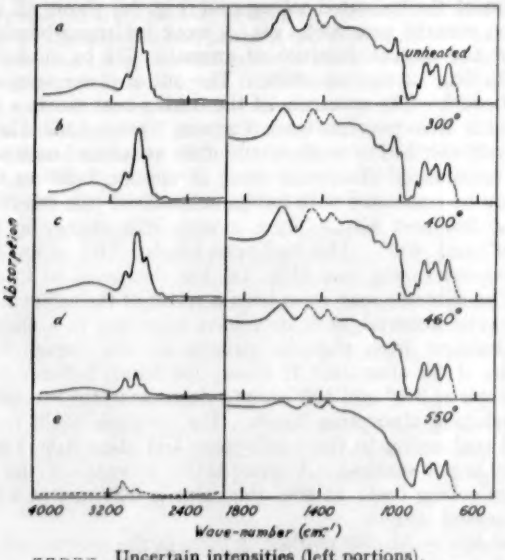
(c) *Coals heated at 460°.*—At 460° marked changes in the spectra are apparent. There is a very pronounced decrease in the intensity of the aliphatic CH stretching absorption bands in the spectra of both coals (Figs. 1*d* and 2*d*). The $D_{ar.}/D_{al.}$ ratios have been estimated for the two products; in each case the value is near 1. A further decrease in

FIG. 1. *Infrared spectra of a carbonised caking coal (Ellington High Main).*



– – – – – Uncertain intensities (left portions).
– – – – – Nujol absorption bands (right portions).

FIG. 2. *Infrared spectra of a carbonised coking coal (South Garsfield Victoria Seam).*



– – – – – Uncertain intensities (left portions).
– – – – – Nujol absorption bands (right portions).

intensity of the hydrogen-bonded OH absorption band occurs in the spectrum of the weakly caking coal (Fig. 1*d*); it is accompanied by a shift in frequency of one of the aromatic CH bending absorption bands at 862 cm.$^{-1}$ in the spectrum of the coal at 400° to 870 cm.$^{-1}$ at 460°. A slight increase in intensity of the 750-cm.$^{-1}$ absorption band is also observed. There are no corresponding changes in the spectrum of the coking coal, although a decrease in intensity of several absorption bands in the region 1100—900 cm.$^{-1}$ (in particular, that at 1030 cm.$^{-1}$) is apparent. Both the caking- and the coking-coal spectra show an increase in the structureless background absorption which, from a previous discussion of the effect (preceding paper), is interpreted as indicating a growth in size of the aromatic lamellæ.

At 460°, the caking coal had contracted and agglomerated; the coking coal, in contrast, had swollen and was in the initial stages of forming a semi-coke. The spectrum of the caking coal shows that hydrogen-bonded OH groups still formed a significant part of the structure, whereas they were in very small concentration in the coking coal. It is possible that hydroxylic material (probably mainly phenolic) in the caking coal during the caking process (*i.e.*, between 400° and 460°) was responsible for the difference in the physical changes which occurred. The simple explanation that the strong intermolecular forces associated with hydrogen-bonding restricted the ability of the caking coal to become plastic and swell is not satisfactory as it is not in accord with a number of facts known about the coking process (*e.g.*, the destruction of coking power by solvent extraction).

(d) *Coals heated at* 550°.—At 550° there is a further marked decrease in the intensity of the aliphatic CH stretching absorption bands; in both spectra (Figs. 1*e* and 2*e*) they are very weak. Further, the hydrogen-bonded OH absorption band has disappeared from the spectrum of the Northumberland coal (Fig. 1*e*) and thus the difference between the two coals in this respect is eliminated. The disappearance of OH groups from the weakly caking coal is accompanied by a marked change in the pattern of absorption between 900 and 700 cm.$^{-1}$. There is an overall increase in intensity, and the 750-cm.$^{-1}$ absorption has now become of approximately the same strength as the other two main absorption bands in this region. Also, the 870-cm.$^{-1}$ absorption band (present in the spectrum of the coal at 460°) has moved to 876 cm.$^{-1}$. The changes in the region 900—700 cm.$^{-1}$ are very similar to those observed in the spectra of a range of unheated vitrains (preceding paper) where they were correlated with the disappearance of phenolic OH groups from the structure; thus the two observations are in good agreement.

The coking coal spectrum (Fig. 2*e*) shows less change between 460° and 550° because there were insufficient OH groups present in the structure to produce, on their elimination, any appreciable change in position of the aromatic CH absorption bands.

The level of background absorption in both spectra has increased; in the caking coal heated to 550° it is similar to that of unheated coals with carbon contents in the range 90—93% (coking ⟶ dry steam coals). In the coking coal spectrum the level corresponds closely to that observed in unheated anthracites (94% of carbon). The higher level of background absorption in the coking coal spectrum indicates, on the previous interpretation of the effect (preceding paper), a larger graphitic crystallite size. The spectrum of the heated coking coal resembles that of an unheated anthracite, not only in the background level but also in the weakness of the aliphatic CH stretching absorption bands and the almost structureless nature of the absorption at frequencies above 1000 cm.$^{-1}$. The similarity suggests that the formation of anthracites may have occurred at temperatures in the region of 500°. Measurements of H/C and O/C ratios of carbonised semi-anthracites (van Krevelen, *Fuel*, 1951, **30**, 253) show that these follow the same course as that observed in the coalification process, and therefore provide some support for the above conclusion.

(e) *Coals heated at* 800°.—No spectra are shown for the coals heated to 800°, for the samples were opaque to infra-red radiation throughout the region 4000—650 cm.$^{-1}$, even in very thin sections. A similar effect has been observed for mulls of powdered graphite (Cannon, *loc. cit.*); in both cases the structureless background absorption extends across the spectrum and no absorption edge is observed. This suggests that between 550° and 800° some graphitisation has occurred. Electrical resistance measurements of coals

carbonised in the above temperature range (Sandor, Proc. Conf., etc., *loc. cit.*, p. 342) also support this view.

(f) *Constant Features of the Spectra.*—The previous discussion has concentrated mainly on the *changes* that occur in coal structure at different temperatures. Two features of the spectra undergo remarkably little change. One is the pronounced 1600 cm.$^{-1}$ absorption band which occurs in the spectra of both coals. In the preceding paper the intensity of this absorption band was ascribed to the presence of oxygen in aromatic ether linkages or in hydroxylated quinone structures. The present work shows that, whatever type of oxygen grouping is associated with the strong 1600-cm.$^{-1}$ absorption band, this grouping must be a very stable one. The second feature occurs only in the spectrum of the Durham coking coal; this is the pattern of absorption bands between 900 and 700 cm.$^{-1}$ which shows very little variation in shape or intensity throughout the range of temperatures. This is surprising because, as stated earlier, the intensity of the aliphatic (or alicyclic) CH stretching absorption bands decreases very markedly in the spectra of samples heated at temperatures above 400°; they are very weak in the spectrum of the 550° sample. Two alternative suggestions can account for these observations: (i) the aliphatic (or alicyclic) material does not form a major part of the structure, but occurs only in units of low molecular weight. Either the spectrum of these units is very similar in the region 900—700 cm.$^{-1}$ to that of the rest of the coal, or it is completely masked by it. On being heated to 550°, the material of low molecular weight is distilled away and leaves aromatic systems largely unsubstituted. In the second alternative (ii) the aliphatic material is associated with the main part of the coal structure and is decomposed on heating. The removal of the aliphatic material leaves unsatisfied valencies on the edges of the aromatic systems, which, however, are not replaced by hydrogen atoms (causing a change in the pattern between 700 and 900 cm.$^{-1}$) but principally by C–C bonds, *i.e.*, the systems become cross-linked.

Evidence from the spectra of solvent extracts (Brown, unpublished work) suggests that aliphatic (or alicyclic) material forms part of the main coal structure, and therefore, at the present stage, explanation (ii) is the more acceptable. This means that, in the temperature range 400—550°, cross-linking of the aromatic systems is initiated.

Independently of the foregoing evidence, the infra-red data suggest strongly that cross-linking occurs at temperatures higher than 550°. Both spectra show that the amount of aliphatic (or alicyclic) material is very small, and yet, as the temperature is increased the H/C ratio continues to fall (van Krevelen, *loc. cit.*); the decrease in the ratio presumably arises from the elimination of hydrogen from the ring systems during the linking process.

Conclusions.—The above analysis shows that coals undergo not only marked physical changes but also important modifications in chemical structure in the temperature range 400—550°. Aliphatic (or alicyclic) material is removed, most probably by simple distillation and chemical decomposition; hydrogen-bonded phenolic OH groups are also eliminated, the change being most marked in the temperature range 460—550°. The data suggest that the formation of C–C cross-links between the aromatic systems accompanies the loss of aliphatic groups, and that at temperatures above 550° the process is continued with the removal of aromatic hydrogen. Presumably, as the temperature is increased, cross-linking extends throughout the structure; the very steep fall in the electrical resistance of coals carbonised at temperatures between 600° and 650° may be a consequence of this change. The opacity of the specimens heated to 800° suggests that some graphitisation has occurred.

Van Krevelen (*Fuel*, 1951, **30**, 253) considers the essential mechanism in the pyrolysis of coal to be a slow primary decomposition which reaches a maximum rate between 400° and 460°; this decomposition comes to an end at about 550°. A secondary reaction then sets in during which hydrogen is split off. This view, which is supported by kinetic studies, is given further significance by the present infra-red work; this suggests that the secondary reaction is a cross-linking of the aromatic systems which results in some graphitisation as the temperature is increased.

A difference between the structure of the caking and coking coal has been found which is apparent in the unheated specimens. This is that hydroxylic material (probably

mainly phenolic) is in much higher concentration in the caking coal. Previous infra-red work on unheated coals (preceding paper) has shown that the development of coking properties is accompanied by a decrease in the amount of hydroxylic material in the structure. The present studies show that this material persists in the temperature range 400—460° and may be an important factor in determining the different physical changes which occur in caking and coking coals.

This work is part of a research programme undertaken by the Chemistry Department of the British Coal Utilisation Research Association and is published by permission of the Director General. The author thanks Mr. R. L. Bond of B.C.U.R.A. for preparing the samples of carbonised coals. He is also indebted to Dr. I. G. C. Dryden for valuable discussions of the carbonisation process, Dr. P. B. Hirsch for stimulating and constructive criticism of the results, and Dr. N. Sheppard for his continued interest throughout the course of the research. The work was carried out in the Department of Colloid Science, Cambridge, by kind permission of Professor F. J. W. Roughton, F.R.S.

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Sorption and Reactivity of Nitrous Oxide and Nitric Oxide in Crystalline and Amorphous Siliceous Sorbents.

By W. E. ADDISON and R. M. BARRER.

[Reprint Order No. 5787.]

Calcium- and sodium-rich forms of chabazite and faujasite, mordenite and a synthetic zeolite with mordenite-like molecular-sieve properties, Vycor porous glass, a sodium aluminosilicate gel (Doucil), and a silica gel have been characterised as sorbents by using oxygen and argon as sorbates. These siliceous sorbents were then used in studies of the sorption of nitric oxide, and, in the case of chabazite, of nitrous oxide.

In chabazite nitrous oxide was stable up to 350°, in contrast to its behaviour when sorbed on certain oxides. Isosteric heats and excess entropies of the adsorbed gas decreased as v/v_m increased. In contrast to the stability of sorbed nitrous oxide, nitric oxide occluded by the crystalline zeolites underwent, usually with remarkable ease and nearly to completion (*e.g.*, in calcium- and sodium-rich faujasites and chabazites), a disproportionation reaction, $4NO = N_2O + N_2O_3$. In porous glass, sodium aluminosilicate gel, and silica gel sorption was less copious, and only in the first two sorbents at 0° was a limited disproportionation observed. There is thus a wide difference between the catalytic activity of the amorphous and the crystalline sorbents.

When nitric oxide was first sorbed in chabazite, porous glass, or the sodium aluminosilicate gel and then oxygen was also occluded, the nitric oxide remained wholly inactive to the oxygen. Occluded dinitrogen trioxide, formed by disproportionation of nitric oxide, liberated nitric oxide from chabazite at 150°, but the nitrogen dioxide also produced was tenaciously retained below 200°. The presence of intracrystalline NO_2^- and NO_3^- was also demonstrated, and ascribed to a side reaction with residual intracrystalline water ($N_2O_3 + H_2O = 2HNO_2$; $N_2O_4 + H_2O = HNO_2 + HNO_3$).

When charcoal was used as sorbent, nitric oxide underwent a different reaction, probably $4NO = N_2 + 2NO_2$.

MOLECULES sorbed in an intracrystalline environment may show unusual chemical reactivity. Hydrogen sulphide and ethylene sorbed in potassium benzenesulphonate form ethanethiol (Lange and Lewin, *Ber.*, 1930, **63**, 2156); in the same sorbent thiophen reacts with the sulphonate at 70° or above (Barrer, Drake, and Whittam, unpublished observation, see *Proc. Roy. Soc.*, 1953, **219** *A*, 32). Baba (*Bull. Chem. Soc. Japan*, 1930, **5**, 190) showed that carbon disulphide in chabazite turned the sorbent yellow and gave off hydrogen sulphide. He considered that this might be due to reaction between carbon disulphide

and residual intracrystalline water. Following observations by Grandjean (*Bull. Soc. franç. Min.*, 1910, **33**, 5) and Wyart (*ibid.*, 1933, **56**, 81, 142), Barrer and Woodhead (*Trans. Faraday Soc.*, 1948, **44**, 1001) found that oxygen reacted with mercury sorbed in chabazite, giving a yellow tint to the chabazite. The sorbent turned black on exposure to moist air, and gave deep colours also with other electron-donor molecules (sulphur dioxide, ammonia, and hydrogen sulphide). It was suggested that an array of mercury and oxygen ions was formed interstitially and that mercury ions could further co-ordinate with the water or other molecules.

Zeolites can also exhibit dehydrohalogenating powers. Thus Barrer and Brook (*ibid.*, 1953, **49**, 940) found that sorption of trifluoro- or chlorodifluoro-methane in chabazite was an irreversible process in which the sorbent was attacked and gradually rendered amorphous and non-sorbing. Hydrothermal extraction of the product aggregated molecularly or ionically dispersed calcium fluoride, formed in the process, into identifiable fluorspar crystals. An initial interstitial liberation of hydrogen fluoride will explain these results. In another instance, hydrogen chloride was smoothly and easily removed from *tert.*-butyl chloride at room temperature, even though the organic molecule was itself too large to enter the crystals. The olefin formed then polymerised to give liquid oils (Barrer and Brook, *Trans. Faraday Soc.*, 1953, **49**, 940). With the secondary chloride, *iso*propyl chloride, which again could not penetrate the crystals, this removal of hydrogen chloride did not occur until about 200°, and even then was very slow; with chloroform, also too large to be occluded, no dehydrochlorination at all could be detected. The hydrogen chloride liberated from *tert.*-butyl chloride was occluded in large amount, and formed some interstitial calcium chloride together with the hydrogen-form of chabazite. No structural change of the lattice was however observed.

A different kind of intracrystalline reaction was noted by Barrer (*Nature*, 1949, **164**, 112), who found that ammonia could be burned away (as nitrogen and water) from the ammonium forms of chabazite and mordenite by oxygen occluded at about 330°. The products were crystalline hydrogen zeolites which, like the parent crystals, were excellent molecular-sieve sorbents (*idem, ibid.*, p. 112).

Considerable interest may therefore attach to reactions induced by or involving zeolites, especially where these processes occur in an intracrystalline environment. The present paper describes the sorption and reactivity of nitrous and nitric oxide in various siliceous sorbents, both crystalline and amorphous. The results add to knowledge of intracrystalline behaviour, especially as regards nitric oxide.

Experimental

Helium (used for dead-space determinations), argon, and oxygen were supplied pure by the British Oxygen Co. Ltd. Nitrous oxide, also obtained from this source, was condensed, and residual gases were pumped away; it was then fractionated, and the vapour density of the pure fraction determined by weighing (Found: 22·02. Calc.: 22·01). Nitric oxide was prepared by Chrétien and Longi's method (*Compt. rend.*, 1943, **217**, 504); it was then fractionated until the product had a satisfactory vapour density. The gas was prepared on two occasions, in 4-l. quantities. Vapour densities found were 14·98 and 14·95 (Calc. for NO: 15·00).

Gas-volumetric sorption methods (Barrer and Brook, *Trans. Faraday Soc.*, 1953, **49**, 940) were employed in the subsequent studies. The apparatus was designed to work in triplicate, there being three sorption bulbs each with associated gas burettes, Toepler pumps, pressure gauges, and gas-supply trains. *X*-Ray examination of some of the sorbents was carried out with a Hilger HRX *X*-ray unit and filtered Cu-K_α radiation. As low-temperature baths for the sorbent bulbs liquid nitrogen (−195°), liquid oxygen (−183°), solid carbon dioxide (−78°), melting chloroform (−63·5°), melting carbon tetrachloride (−22·5°), and ice (0°) were used. For higher temperatures, electrical heating of the sorbent was employed.

In quantitative analysis of binary gas mixtures, and in tests of purity of single gases, the determination of vapour density by direct weighing of gas samples at known pressures was extensively employed. This method was normally very satisfactory indeed for the systems studied.

All sorbents were outgassed for 24 hr. at the temperatures given in parentheses. The crystalline sorbents were chabazite (pink and white varieties) (450°), mordenite, faujasite (a

synthetic specimen of composition $Na_2O,Al_2O_3,2{\cdot}6SiO_2,6{\cdot}2H_2O$, and made available by Linde Air Products Co.),[†] a synthetic zeolite, Na–A (as its sodium-form, which exhibits molecular-sieve properties analogous to those of mordenite; also supplied by Linde Air Products Co.) (all 350°). These zeolites represent a group of molecular-sieve crystals in which the order of openness is sodium- and calcium-faujasite > calcium-chabazite > sodium-chabazite, mordenite, and synthetic zeolite (Na–A). Faujasite is so open in structure that it readily occludes *neo*pentane (Barrer, unpublished observation).

Sodium-rich chabazite was prepared from calcium-rich natural chabazite by successive treatments with concentrated aqueous sodium chloride and heating on a steam-bath. After three treatments no more calcium could be detected in the mother-liquor, and the crystals were thoroughly washed and stored for use. Calcium-rich faujasite was made in the same way from the synthetic sodium-form by use of aqueous calcium chloride.

Amorphous sorbents employed were porous glass (supplied by the Corning Glass Co., in the form of rod; the composition was approximately SiO_2, 96%; B_2O_3, 4% with very little Al_2O_3 and Na_2O). Sections of rod were ground, and the powder degassed (200°). "Doucil" sodium aluminosilicate water-softener was available commercially. It was ground to powder and outgassed (200°). Silica gel was supplied by B.D.H. Ltd., as employed for desiccation. The particle size was between 30 and 120 mesh. It was ground and outgassed (290°). An activated sorbent charcoal was also supplied by B.D.H. Ltd. and was likewise ground and outgassed (300°).

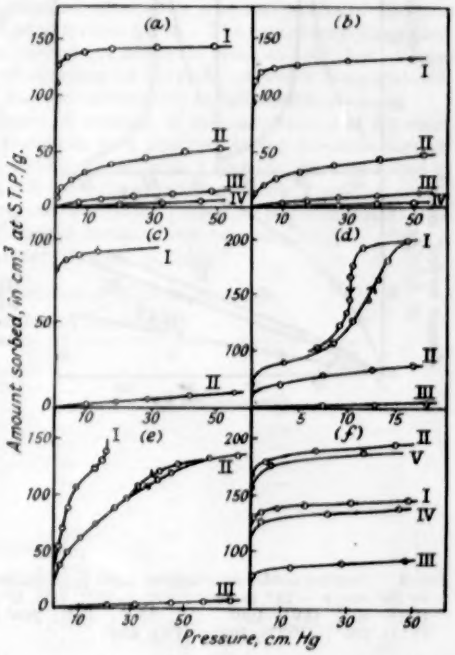


FIG. 1. *Characteristic isotherms in siliceous sorbents.*

(*a*) Oxygen in chabazite: (I), −183°; (II), −78°; (III), 0°; (IV), 50°.
(*b*) Argon in chabazite: (I), −183°; (II), −78°; (III), 0°; (IV), 50°.
(*c*) Oxygen in mordenite: (I), −183°; (II), 0°.
(*d*) Oxygen in porous glass: (I), −193·9°; (II), −183°; (III), −78°.
(*e*) Oxygen in Doucil aluminosilicate gel: (I), −194·4°; (II), −183°; (III), −78°.
(*f*) Curve (I), Oxygen at −183° in chabazite (Ca-rich); (II), Oxygen at −183° in Ca-faujasite; (III), Oxygen at −183° in Na-chabazite; (IV), Oxygen at −183° in synthetic zeolite ("Na–A"); V), Oxygen at −183° in Na-faujasite.

Characterisation of the Sorbents.—Before investigation of the sorption of nitrous and nitric oxide, the sorbents, some of which have previously been little studied (*e.g.*, faujasite, Na–A, and Doucil), were characterised and compared by a study of oxygen and argon sorption. Typical isotherms are shown in Fig. 1.

Faujasites (sodium- and calcium-forms) show saturation values for oxygen approaching 200 cm.³ (at S.T.P.)/g.; in calcium-chabazite and in Na–A this figure is about 150 cm.³. Sodium-rich chabazite and mordenite give saturation values approaching 100 cm.³. Saturation values for argon are rather less in all cases investigated. Evidently faujasite surpasses all the other zeolites not only in openness of the framework but also in the amount of interstitial volume available for sorption. Sorption at −78° was still substantial in chabazite and in faujasite, but at higher temperatures the sorption falls off rapidly. In all the crystalline

zeolites the isotherms are of Type I in Brunauer's classification (" Physical Adsorption of Gases and Vapours," Oxford University Press, 1945, p. 150), a situation arising because in no case are the channels traversing the crystals, in which occlusion occurs, sufficiently wide for capillary condensate or multilayers to appear.

Interesting changes occur in the character of the isotherms in porous glass and in Doucil. Here, crystalline character has disappeared, capillaries are wider and, unlike those in zeolites, show a considerable range in sizes. As a result capillary condensate appears at higher relative

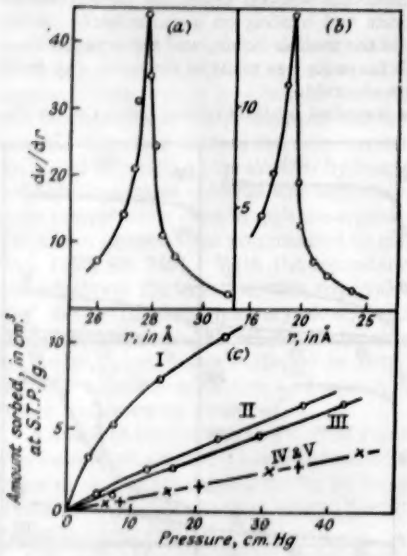


FIG. 2. *Pore-size distributions in (a) porous glass and (b) " Doucil " aluminosilicate gel.*

FIG. 2 (*c*). *Degree of selectivity shown between several zeolites and between* Ca- *and* Na-*forms of zeolite, in the sorption of oxygen at* 0°.

(I) and (II), a Ca- and a Na-chabazite respectively. (III) and (IV; points marked x), Ca- and Na-faujasites, respectively. (V), Synthetic zeolite " Na-A " (points marked +).

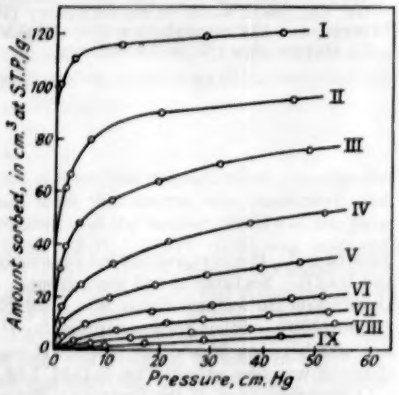


FIG. 3. *Sorption isotherms of nitrous oxide in chabazite in the range* −78° *to* 350°: (I), −78°; (II), 0°; (III), 50°; (IV), 100°; (V), 150°; (VI), 200°; (VII), 250°; (VIII), 300°; (IX), 350°

pressures, with associated hysteresis loops and isotherms which are (for porous glass) or tend to be (for Doucil) of Type IV in Brunauer's classification. By applying Kelvin's equation to the desorption branch of the isotherms the pore-size distributions of Figs. 2*a* and 2*b* were obtained (Foster, *Discuss. Faraday Soc.*, 1948, **3**, 41). Porous glass gives a narrower distribution of sizes than does Doucil, but the maximum in the curve of dv/dr against r occurs at a larger value of r (~27 Å) for porous glass than for Doucil (~20 Å). In these calculations the thickness of the adsorbed layer remaining when the meniscus just disappears is taken into account (*idem*, *ibid.*; Barrer and Barrie, *Proc. Roy. Soc.*, 1952, **213**, *A*, 250).

The affinity between oxygen and the sorbent varies according to the cation present. Fig. 2*c* shows that the affinity of oxygen is greater for the calcium- than for the sodium-form of faujasite

and of chabazite (in the latter allowance is made for the different saturation values). These differences in affinity almost certainly arise from different heats of sorption among the cationic forms (Barrer, *Trans. Faraday Soc.*, **1944**, **40**, 555; Barrer and Riley, *ibid.*, **1950**, **46**, 853).

It is evident from the data presented that in the above sorbents, together with the B.D.H. silica gel, one has a diverse group of siliceous sorbents from the viewpoints both of chemical composition and of physical structure and porosity.

Sorption of Nitrous Oxide.—The nitrous oxide molecule (m. p. −90·9°; b. p. −88·5°; dipole moment, 0·17 D) is linear in form and has very similar physical properties to carbon dioxide. As would be expected from this, nitrous oxide was sorbed much more strongly than oxygen or argon, so sorption was investigated between −78° and 350° (Fig. 3).

At higher temperatures nitrous oxide can be decomposed catalytically into its elements (Dell, Stone, and Tilley, *ibid.*, **1953**, **49**, 201; Amphlett, *ibid.*, **1954**, **50**, 273). However, no such decomposition occurred in chabazite up to 350°, since the high-temperature isotherms were reversible. Moreover, the desorbed gas was retained after each sorption isotherm and the vapour density was measured and shown to be that of nitrous oxide. The rate of sorption varied with temperature: not more than 10 min. was needed per isotherm point at 350°, but at least 3—4 days were needed at −78°. Because of slowness of sorption at lower temperatures, isotherms at −78°, and possibly at 0° and 50°, may not correspond to full equilibration.

Thermodynamic Considerations.—Isosteric heats of sorption of nitrous oxide, and for comparison those of oxygen, were determined in chabazite as a function of the amounts sorbed. These heats, obtained from smoothed isosteres, are shown in Table 1 and Fig. 4*c*. As noted in the previous section, there may be an error in ΔH for nitrous oxide in Table 1, cols. 6 and 7, owing to the slow rate of equilibration at the lowest temperatures. Another factor of importance is temperature control, which in the high-temperature furnaces was accurate to ±1°, giving a maximum variation of 4% for the temperature interval of 50° in Table 1.

TABLE 1. *Isosteric heats of sorption of N_2O in chabazite.*

v (cm.³ at S.T.P./g.)	ΔH (cal./mole) over range *						
	1	2	3	4	5	6	7
1	15,260	15,410	15,280	—	—	—	—
2	15,130	15,230	14,940	—	—	—	—
3	15,000	15,090	14,870	—	—	—	—
4	14,670	14,920	14,740	—	—	—	—
5	14,540	14,330	14,440	—	—	—	—
6	14,210	14,030	13,860	—	—	—	—
7	14,030	13,750	13,270	—	—	—	—
8	—	13,490	12,610	—	—	—	—
9	—	13,220	11,930	—	—	—	—
10	—	12,970	11,460	11,620	—	—	—
11	—	—	10,980	11,570	—	—	—
12	—	—	10,700	11,520	—	—	—
15	—	—	—	11,370	11,250	—	—
18	—	—	—	11,180	10,080	—	—
20	—	—	—	11,080	9,540	—	—
22	—	—	—	11,040	9,490	—	—
25	—	—	—	—	9,300	—	—
28	—	—	—	—	9,240	—	—
30	—	—	—	—	9,270	11,090	—
32	—	—	—	—	9,100	11,000	—
35	—	—	—	—	9,220	10,970	—
38	—	—	—	—	9,410	10,950	—
40	—	—	—	—	—	10,640	—
42	—	—	—	—	—	10,240	—
45	—	—	—	—	—	10,210	—
48	—	—	—	—	—	10,180	—
50	—	—	—	—	—	10,150	9850
52	—	—	—	—	—	9,890	9520
55	—	—	—	—	—	9,860	9310
60	—	—	—	—	—	—	9220

* Where the temperature ranges for which these values are quoted are as follows: (1) 300—350°, (2) 250—300°, (3) 200—250°, (4) 150—200°, (5) 100—150°, (6) 50—100°, (7) 0—50°.

The main interests of the data were the high heat of sorption of nitrous oxide, and the way in which ΔH for both gases decreased at first rapidly and then very slowly as the charge of sorbate rises. The initial change in the isosteric heat with amount sorbed outweighs any temperature coefficient in ΔH. The partial molar entropies of the sorbed nitrous oxide were determined as

functions of the amount, only the isotherms between 200° and 350° being used, for ΔH in Table 1 is most consistent at this high-temperature end of the measurements.

The standard state of the gas was taken as 1 atm. At 298° K the standard entropy S^{+G} of nitrous oxide is 51·44 e.u. (Blue and Giauque, *J. Amer. Chem. Soc.*, 1935, **57**, 991), and from Kassel's heat-capacity data (*ibid.*, 1954, **56**, 1838) the standard entropy at any other temperature was determined by graphical integration ($S^{+G}_2 - S^{+G}_1 = 2{\cdot}303 \int_{T_1}^{T_2} C_p \, \mathrm{d} \ln T$). For the isothermal transfer of a mole of gaseous sorbate from the gas phase to an infinite amount of the sorbent–sorbate system over which the equilibrium pressure is p_Γ and the sorbate concentration Γ one has:

$$\Delta\mu^+_\Gamma = \overline{\Delta H}^+_\Gamma - T\overline{\Delta S}^+_\Gamma = \boldsymbol{R}T \ln p_\Gamma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\Delta\mu^+_\Gamma = \mu^\sigma_\Gamma - \mu^{+G}$ is the difference in the chemical potential of sorbate in the standard state in the gaseous phase (μ^{+G}) and the chemical potential of sorbate at concentration Γ in or

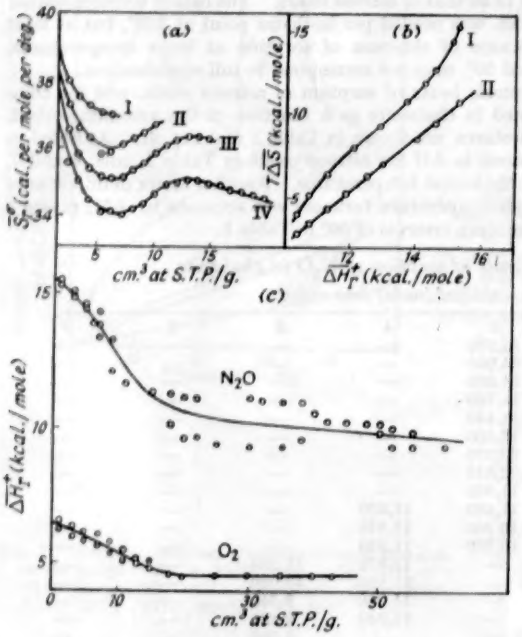


FIG. 4. *(a) Partial molar entropy of nitrous oxide, occluded by chabazite, as a function of temperature and of amount sorbed*: (I), 350°; (II), 300°; (III), 250°; (IV), 200°.

(b) The relations between the excess entropy of sorption, $\overline{\Delta S}^*_\Gamma$ (Curve I), and the standard differential entropy of sorption, $\overline{\Delta S}^+_\Gamma$ (Curve II), and the isosteric sorption heat, $\overline{\Delta H}^+_\Gamma$.

(c) The relation between $\overline{\Delta H}^+_\Gamma$ and amount sorbed for nitrous oxide and for oxygen in chabazite.

on the sorbent. Similarly $\overline{\Delta H}^+_\Gamma = \overline{H}^\sigma_\Gamma - H^{+G}$ is the isosteric heat of sorption, given by $\overline{\Delta H}^+_\Gamma = \boldsymbol{R}T^2 \, \partial \ln p_\Gamma / \partial T$ (ΔH in Table 1). Finally, $\overline{\Delta S}^+_\Gamma = \overline{S}^\sigma_\Gamma - S^{+G}$ is the differential molar entropy of transfer of sorbate from gas phase to an infinite amount of sorbent–sorbate system in which sorbate has a concentration Γ. $\overline{H}^\sigma_\Gamma$ and $\overline{S}^\sigma_\Gamma$ are the partial molar heat and entropy of sorbate in or on the sorbent and H^{+G} and S^{+G} are the standard heat content and entropy of the gaseous sorbate. In the nomenclature, we have followed the symbols used by Everett (*Trans. Faraday Soc.*, 1950, **46**, 453, 942, 957).

From equation 1 we obtain:

$$\overline{S}^\sigma_\Gamma = S^{+G} + (\overline{\Delta H}^+_\Gamma / T) - \boldsymbol{R} \ln p_\Gamma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Since all the terms on the right-hand side of equation (2) are available, $\overline{S}^\sigma_\Gamma$ can be derived. These partial molar entropies of the sorbed nitrous oxide are shown in Fig. 4*a* as a function of the volume V sorbed (in c.c. at S.T.P./g.). The values of $\overline{S}^\sigma_\Gamma$ are substantial and increase, as might be expected, with rising temperature. The presence of minima is interesting, but in view of the large values of $\overline{S}^\sigma_\Gamma$ and of possible limitations in their accuracy any significance of the relatively shallow minima should not be emphasised.

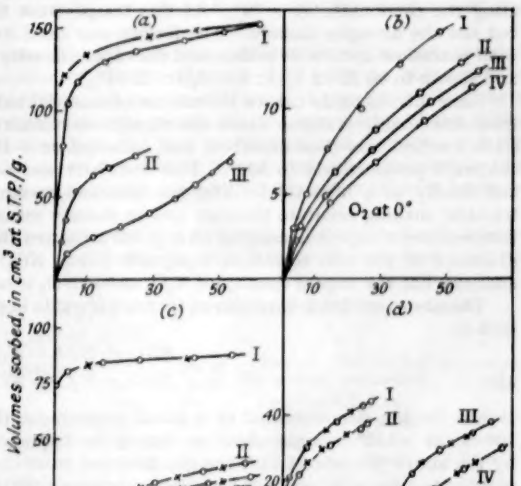
According to the model for localised Langmuir sorption, the differential configurational entropy $\bar{S}^{a,l}{}_{\Gamma} = -R \ln \theta/(1-\theta)$. By subtracting this quantity from $\Delta S^{+}{}_{\Gamma}$, obtained from equation (1), $\overline{\Delta S}^{*}{}_{\Gamma}$, the excess differential molar entropy of sorption, may be obtained. This entropy is associated directly with the loss of mobility when the gas is transferred from the gas phase to the sorbed phase. When $T\overline{\Delta S}^{*}{}_{\Gamma}$ is plotted against $\Delta H^{+}{}_{\Gamma}$, the graph is nearly linear (Fig. 4*b*). A similar relation was observed in the adsorption of a number of substances on charcoal (Everett, *loc. cit.*, p. 959), and was there regarded as compatible with a localised sorption in which there were departures from the ideal Langmuir model due to a simultaneous variation of both heat and entropy of sorption. In the calculations of Fig. 4*b*, V_m was taken as 130 cm.³ at S.T.P./g., and the standard state in the gas phase was 1 mm. pressure.

FIG. 5. (*a*) *Sorption of* NO *in chabazite and mordenite.*
—○—, Adsorption points.
—×—, Desorption points.
(I) Chabazite at 0°; (II) mordenite at 0°; (III) chabazite at 100°.

(*b*) *Decrease in sorption of oxygen by chabazite at* 0° *after prior sorption of nitric oxide followed by thorough outgassing.*
(I), Oxygen uptake on fresh sorbent; (II), oxygen uptake after one treatment with nitric oxide; (III), oxygen uptake after two treatments with nitric oxide; (IV), oxygen uptake after three treatments with nitric oxide.

(*c*) *Sorption of oxygen and argon by chabazite after first sorbing the quantities of nitric oxide given in parentheses.*
—○—, Adsorption points.
—×—, Desorption points.
(I), O_2 at −183° (46·0); (II), O_2 at −78° (19·74); (III), A at −78° (19·74); (IV), O_2 at 0° (14·80); (V), O_2 at 50° (9·79).

(*d*) *Sorption of oxygen and argon in porous glass (Curves I and III respectively), and in porous glass after first sorbing* 19·49 *cm.*³ *at S.T.P./g. of nitric oxide (Curves II and IV respectively).*
All isotherms are at −183°.
—○—, Adsorption points.
—×—, Desorption points.



Similar calculations were made for oxygen at −63·5°, assuming $V_m = 150$ cm.³ at S.T.P./g. Here for $\theta > 0{\cdot}1$, $\overline{\Delta H}^{+}{}_{\Gamma}$ and $T\overline{\Delta S}^{*}{}_{\Gamma}$ were nearly constant. Even for $\theta < 0{\cdot}1$, plots of $\overline{\Delta H}^{+}{}_{\Gamma}$ and $T\overline{\Delta S}^{*}{}_{\Gamma}$ against the amount sorbed followed parallel courses.

That a linear correlation between $\overline{\Delta H}^{+}{}_{\Gamma}$ and $T\overline{\Delta S}^{*}{}_{\Gamma}$ can best be interpreted as a localised sorption does not seem wholly convincing. However, localised sorption will always tend to be favoured when the heat of sorption decreases as θ increases, because the site heterogeneity will lead to anchoring of molecules to the most energetically sorbing sites.

Sorption of Nitric Oxide.—The sorption of nitric oxide (m. p. −163·7°; b. p. −151·8°; dipole moment 0·17 D) was first studied on chabazite at 0° and 100° and on mordenite at 0° (Fig. 5*a*). Sorption was clearly abnormal: a very large amount of nitric oxide was occluded for a gas of the above physical properties at the experimental temperatures; the sorption showed a slow drift and was irreversible as indicated by the desorption points in chabazite at 0° (Fig. 5*a*). The gas from this isotherm was then desorbed and collected in five fractions by freezing at −183°. The first fraction consisted of the gas present in the gas phase. With the exception of about 20%, the second fraction consisted of products desorbed directly from the chabazite, while for the other fractions the desorbate all came substantially from the chabazite. The fourth and the fifth desorption required heating of the sorbent to 100°. Vapour densities of the fractions then were: Fraction (1) 17·51; (2) 19·04; (3) 20·32; (4) 17·91; (5) 18·02. Thus the desorbate

contains a gas or gases heavier than nitric oxide (vapour density, 15·00) and, from the variable vapour density, is a mixture of changing composition.

Each fraction was colourless and had a vapour pressure close to 2·7 mm. at −183°, *i.e.*, that of pure nitric oxide, thus indicating the presence of that gas. When air was admitted to each fraction, after completion of vapour-density measurements, the formation of brown nitrogen dioxide was observed.

From consideration of the starting material and of the above behaviour, the gas or gases in admixture with nitric oxide must (1) contain only the elements oxygen and nitrogen; (2) be of substantially higher molecular weight than nitric oxide; (3) have negligible vapour pressure at −183°; and (4) be colourless whether solid or gas. Only nitrous oxide fulfils these conditions, and the desorbate must be a binary mixture of this with nitric oxide. The presence of nitrous oxide was established by oxidising all the nitric oxide to nitrogen dioxide with excess of air, freezing at −183°, pumping away incondensibles (nitrogen and excess of oxygen), and fractionating the condensate at −78°. At this temperature the presumed nitrous oxide evaporated but not the nitrogen dioxide. The former was freed from any traces of the latter by contact with potassium hydroxide pellets, and the vapour density of the colourless gas was then measured and shown to be 22·02 (Calc. for N_2O: 22·01%).

Since nitrous oxide cannot for reasons of material balance be the sole decomposition product from nitric oxide, a higher oxide was thought to remain occluded in chabazite even at 100°. A sixth fraction was then desorbed, and collected at −183°, by raising the temperature of the chabazite progressively to 400°. This desorbate was a brown gas condensing to a blue liquid and finally to a blue solid. The gas attacked mercury (cf. nitrogen dioxide or dinitrogen trioxide) making accurate pressure and so density measurements difficult. However, at room temperature a vapour density of 35·8 ± 0·3 indicated that the gas contained nitric oxide. The existence of the two equilibria $N_2O_3 \rightleftharpoons NO + NO_2$ and $N_2O_4 \rightleftharpoons 2NO_2$ prevents further analysis, but the vapour density of $N_2O_4 \rightleftharpoons 2NO_2$ is *ca.* 42·6 at room temperature.

The above evidence then shows that nitric oxide in chabazite undergoes disproportionations such as

$$4NO = N_2O + N_2O_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$3NO = N_2O + NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It was further demonstrated in a blank experiment that merely condensing nitric oxide for 100 hr. at −183° brought about no detectable disproportionation. Finally, it was established by the above procedures that the gas desorbed from chabazite after sorption at 100° and from mordenite after sorption at 0° had also undergone a partial disproportionation.

Disproportionation of Nitric Oxide by Other Siliceous Sorbents and by Charcoal.—The methods developed for chabazite were next applied to porous glass, silica gel, Doucil sodium aluminosilicate gel, and charcoal. The sorption by the three siliceous sorbents at 0° was much less than that in chabazite or mordenite. After 14 days at 0° the vapour density of the desorbate from porous glass was only 15·41, indicating a limited disproportionation. Also, some nitrogen dioxide was desorbed from the porous glass by heating it to 200°. A sorption period of 1 month at 0° (with daily 5-min. intervals at −183° to sorb all gases and help promote reaction) gave little further change, the vapour density being 15·47, while a 5-min. sorption time at −63·5° led to a desorbate of vapour density 15·39. These results show only slight disproportionation and suggest that the products thereof may inhibit further reaction by preferential occupation of the catalytically active centres. With silica gel after 10 days at 0° the desorbate had a vapour density of only 15·11, indicating negligible reaction of the sorbed nitric oxide. Doucil sodium aluminosilicate gel behaved like porous glass; 14 days' sorption at 0° followed by desorption gave a desorbate of vapour density 15·42, and nitrogen dioxide was also liberated when the gel was heated to complete desorption. When the nitric oxide was sorbed on either porous glass or Doucil at −183° and held for long periods at this temperature (~5 weeks) the desorbate had the vapour density of pure nitric oxide, so no detectable reaction had occurred.

It is thus clear that the three amorphous gel sorbents behave similarly in giving only limited or negligible disproportionation of sorbed nitric oxide, in contrast with the extensive disproportionation in chabazite and, as will be shown in the next section, in several other zeolites.

The behaviour of nitric oxide sorbed in charcoal was, however, quite distinct. Charcoal sorbed nitric oxide copiously (*e.g.*, 80 cm.³ at S.T.P./g. at 0° and 54 cm. Hg). A slow pressure drift suggested that an irreversible process was involved, and much of the desorbate was incondensable at −183° The desorbate had a vapour density of 14·78, and when this desorbate was partially condensed overnight at −183°, and the incondensable gas pumped away, the residue

on evaporation yielded a colourless gas of vapour density 15·10. Since this gas also formed brown fumes on exposure to air it was clearly unchanged nitric oxide containing no nitrous oxide. The original lighter and incondensable constituent could only be nitrogen or carbon monoxide (vapour density 14·01). When the charcoal was heated to complete desorption much nitrogen dioxide was evolved. It was therefore considered that in part the nitric oxide was sorbed by charcoal to undergo the disproportionations $4NO = N_2 + 2NO_2$ or $6NO = N_2 + 2N_2O_3$. This behaviour is in agreement with Shah's observations (*J.*, 1929, 2661) but since it differed from the behaviour noted with the siliceous sorbents it was not studied further.

The Extent of Disproportionation of Nitric Oxide Sorbed by Zeolites.—Desorption by freezing the desorbate at −183° with the temperature of the sorbent not above 150° liberated only nitric and nitrous oxide from chabazite and other zeolites. Nitrogen dioxide was not evolved until temperatures of 200° or above were reached. By admitting a measured amount of nitric oxide to the sorbent, followed by desorption below 150°, one may then collect the nitric and nitrous oxide and analyse the binary mixture quantitatively through measurement of gas volumes and vapour-density.

The two possible reaction equations (1) and (2) were differentiated in the case of desorbate from chabazite following sorption of nitric oxide at −183°. On no occasion was an amount of nitrous oxide obtained more than one-quarter of the initial amount of nitric oxide sorbed and usually this amount of nitrous oxide was nearly exactly one-quarter of the initial charge of nitric oxide (cf. Table 2). It thus appeared that reaction (1) was operative and the percentage decompositions of nitric oxide given in Tables 2, 3, and 4 are all calculated on this assumption. It remains possible that at suitably high temperatures reaction (2) may begin to dominate.

In Table 2 are summarised the results of the analyses of the desorbate from chabazite following occlusion of the nitric oxide at −183°. Evidently reaction is virtually complete however

TABLE 2. *Extent of reaction* $4NO = N_2O + N_2O_3$ *in chabazite following sorption of* NO *at* −183°.

No. of run	Time at −183° (hr.)	Dose of NO sorbed (cm.³ at S.T.P./g.)	Vol. of N_2O recovered (cm.³ at S.T.P./g.)	Decompn. of NO, %	No. of run	Time at −183° (hr.)	Dose of NO sorbed (cm.³ at S.T.P./g.)	Vol. of N_2O recovered (cm.³ at S.T.P./g.)	Decompn. of NO, %
1	1/60	49·63	12·14	97·8	5	24	17·06	4·19	98·2
2	24	47·83	11·76	98·3	6	24	93·44	23·32	99·8
3	168	48·86	12·06	98·8	7	24	95·90	23·68	98·8
4	336	50·05	12·35	98·7					

TABLE 3. *Effect of temperature on the reaction* $4NO = N_2O + N_2O_3$ *in chabazite.*

No. of run	Temp.	Time (hr.)	Dose of NO sorbed (cm.³ at S.T.P./g.)	Vol. of N_2O recovered (cm.³ at S.T.P./g.)	Decompn. of NO, %
8	0°	1	16·03	3·18	79·3
9	0	7	14·51	2·91	80·2
10	0	24	16·35	3·16	77·3
11	0	25	16·74	3·31	79·1
12	0	119	14·45	2·91	80·6
13	0	1	10·35	2·01	77·7
14	−22·5	1	24·11	5·29	87·8
15	−63·5	1	24·10	5·70	94·6
16	−78	1	34·48	8·47	98·3
17	−78	31	54·98	13·78	100·2

short the time of contact between nitric oxide and chabazite at −183° and over a wide range in the amount of nitric oxide sorbed.

The effect of the third variable, temperature, upon the extent of decomposition according to equation (1) is shown in Table 3, in which are summarised data for sorption temperatures of nitric oxide of −78°, −63·5°, −22·5°, and 0°. At −78° decomposition is as complete as when sorption occurs at −183°, but the proportion of nitric oxide disproportionated, though always high, is reduced especially at −22·5° and 0°. Runs 8—13 again show that times of contact of nitric oxide with chabazite at 0° of 1—119 hr. have no influence on the extent of reaction.

In the various runs reaction may not occur at the sorption temperature but during heating of the sorbent before desorption. From Table 3 one sees that reaction begins to be incomplete

when the nitric oxide is initially sorbed at $-63{\cdot}5°$ or above, and it is thus probable when sorption was initially at $-78°$ or $-183°$ that the actual disproportionation of nitric oxide must have occurred below $-63{\cdot}5°$.

Information regarding the disproportionation reaction follows also from a detailed consideration of a typical run, *e.g.*, run 2, Table 2. From 47·83 cm.³ of nitric oxide equation (1) requires 11·96 cm.³ of nitrous oxide, in close agreement with 11·76 cm.³ (all at S.T.P.) actually obtained. But the desorptions at 150°, although reaction according to equation (1) was complete and so all the nitric oxide was used up, always gave some nitric oxide in the desorbate. This apparent contradiction is due to the dissociation at 150° of sorbed dinitrogen trioxide: $N_2O_3 = NO + NO_2$. The nitric oxide is liberated but the dioxide is still sorbed. The maximum yield of nitric oxide by dissociation of the trioxide would in run 2, Table 2, be 11·96 cm.³, compared with an actual recovery of 9·57 cm.³.

Because chabazite was so much more effective in catalysing reaction (1) than the amorphous siliceous sorbents (porous glass, Doucil, silica gel), the reaction was studied in other crystalline zeolites in which either the cation was changed ($Na \rightleftharpoons Ca$) or the openness of the aluminosilicate framework was altered, or both. Thus the order of openness among the zeolites studied, based on molecular sieve experiments, was: Na-faujasite, Ca-faujasite > Ca-rich chabazite > Na-rich chabazite, and Na–A. Disproportionation was studied after sorption at 0°, by the procedures used with chabazite. The results given in Table 4 show that all the crystalline zeolites were very effective, the least effective being the less open structure Na–A. Mordenite was also effective in bringing about the reaction (1), but a breakage prevented quantitative results from being obtained.

TABLE 4. *Extent of the reaction* $4NO = N_2O_3 + N_2O$ *following sorption of* NO *at* 0° *in various zeolites.*

Sorbent	Vol. of NO sorbed (cm.³ at S.T.P./g.)	Vol. of N_2O recovered	Reaction, %
Ca-Faujasite	21·45	4·82	89·7
Na-Faujasite	22·50	4·08	72·8—83·6 *
Ca-rich Chabazite	(See Table 3)		79·6
Na-Chabazite	15·68	3·52	89·8—92·7 *
Na–A	16·31	1·07	26·2—42·7 *

* The nitric oxide was not in these cases wholly sorbed. Thus it was uncertain whether the nitrous oxide was produced by decomposition of the entire volume of nitric oxide used or only of that sorbed. Hence figures based on each possibility are given.

Formation of Intracrystalline Nitrite and Nitrate.—After chabazite used in sorbing nitric oxide had been thoroughly outgassed, the sorption of oxygen at 0° was re-determined, and found to be less than in the original crystals. Successive sorptions of nitric oxide each followed by desorption progressively reduced the subsequent sorption of oxygen (Fig. 5*b*). In all these runs the nitric oxide had been admitted at one or more of the temperatures $-183°$, $-78°$, 0°, and 50°. In a second series of experiments nitric oxide was sorbed three times at 250°, the sorbent being outgassed after each sorption and the oxygen uptake at 0° measured. The sorptive capacity of the chabazite towards oxygen was now even more drastically reduced.

Chabazite crystals showing this impaired sorptive capacity still gave the unaltered *X*-ray powder pattern of the original crystals. A sample of chabazite used in the sorption of nitric oxide at 0° was then outgassed for more than 60 hr. at 400—450° to ensure that all oxides of nitrogen would be removed. The sample was then hydrothermally extracted at 170° three times for several days. The extracts evaporated to dryness yielded solids totalling 2·1% by weight of the sample. Another similar experiment, on a different specimen of chabazite, gave a value of 2·4%. The solids were found to contain sodium, calcium, nitrite, and nitrate ions. The data are compatible with the view that dinitrogen trioxide (or nitrogen dioxide) produced by disproportionation of nitric oxide reacts with any residual intracrystalline water either at the sorption temperature or during outgassing: $H_2O + 2NO_2 = HNO_2 + HNO_3$; $H_2O + N_2O_3 = 2HNO_2$. The nitrous and nitric acid then form sodium and calcium nitrite and nitrate by reaction with interstitial cations, and convert the chabazite in part into its hydrogen form. The intracrystalline nitrate and nitrite are then responsible for the impaired sorptive powers of the chabazite.

When the hydrothermally extracted chabazite crystals were re-examined as sorbents they were found to be fully restored as compared with the original crystals (cf. Table 5). Since it

has been shown that crystalline hydrogen chabazite is an excellent sorbent, quite equal to chabazite (Barrer, *Nature*, **1949**, **164**, 112), the recovery shown in Table 5 is as expected for crystals which may be partly H-chabazite but from which occluded nitrite and nitrate have been removed.

TABLE 5. *Sorption of oxygen in original chabazite and in used and extracted chabazite, at 76 cm.*

Sorption temp.	O_2 sorbed (cm.³ at S.T.P./g.) in: unused crystals	used and extracted crystals *	Increase in O_2 sorption, %
−183°	147·2	145·6	−1·09
−78	59·2	62·4	5·4
0	18·06	19·16	6·1
50	8·88	10·53	15·7
100	3·95	4·62	17·0

* Before extraction but after use in sorption of nitric oxide these crystals sorbed only 12·3 cm.³ at S.T.P. of oxygen at 0° and 76 cm.

Reactivity of Sorbed Nitric Oxide towards Oxygen.—At temperatures where oxygen and argon are rather weakly sorbed (*e.g.*, between −78° and 0°), nitric oxide is occluded by chabazite in considerable quantity without giving any measurable gas pressure. Thus sorption of oxygen and of argon can be quantitatively studied in crystals of chabazite suitably charged with nitric oxide. The reaction between gaseous nitric oxide and oxygen proceeds freely and can be measured down to −192° (Briner, Pfeiffer, and Malet, *J. Chim. phys.*, **1924**, **21**, 25), and it was therefore of interest to study the reactivity of sorbed nitric oxide towards oxygen. Disproportionation of sorbed nitric oxide is a complicating factor and it depends on how rapidly and completely this reaction proceeds whether any sorbed nitric oxide is present to undergo oxidation. If some sorbed nitric oxide is present the nature of the sorption can still modify its reactivity, for chemisorption may remove the free-radical character of nitric oxide.

Doses of nitric oxide were admitted to the chabazite in quantity such that no measurable gas pressure developed. This eliminates the possibility of the gas-phase reaction $2NO + O_2 = 2NO_2$. Sorption of oxygen was then investigated; the oxygen was next pumped off without raising the temperature so that no oxide of nitrogen was displaced; and finally the sorption of argon was measured. Typical oxygen and argon isotherms are shown in Fig. 5*c* when the quantities of nitric oxide sorbed at each temperature were those given in Table 6. This table

TABLE 6. *Occlusion of oxygen and argon at* 76 cm. *in* NO-*chabazite.**

Temp. of isotherm	−183°	−78°	0°	50°
Vol. of NO sorbed	46·00	19·74	14·80	9·79
Vol. of O_2 sorbed	86·7	41·1	10·4	4·4
Vol. of O_2 sorbed in absence of NO	147·2	59·2	18·1	8·9
Vol. of A sorbed	—	34·8	9·4	—
Vol. of A sorbed in absence of sorbed NO	—	51·9	16·2	—
Decrease in O_2 sorption, %	41·1	30·6	41·3	50·6
Decrease in A sorption, %	—	32·9	42·4	—

* All volumes are in terms of cm.³ (at S.T.P.)/g.

compares the amount of oxygen and of argon sorbed in presence and in absence of occluded nitric oxide at 76 cm. pressure, at various temperatures and for different amounts of sorbed nitric oxide. The sorptions of oxygen and of argon are reduced by occlusion of nitric oxide in practically the same ratios. Thus there is no evidence of any reaction between oxygen and sorbed nitric oxide. Further convincing evidence of lack of reactivity is afforded by the complete reversibility of the isotherms of oxygen in NO-chabazite. One may conclude either that sorbed nitric oxide has lost its free-radical character or that it has disproportionated completely ($4NO = N_2O + N_2O_3$).

Since porous glass and Doucil are relatively ineffective in disproportionating sorbed nitric oxide, the nitric oxide being desorbed largely unchanged, the procedures used with chabazite to study reactivity of sorbed nitric oxide towards oxygen were extended to these two gels. Essential results are summarised in Table 7. These show that the uptake of nitric oxide again reduces oxygen and argon sorptions in practically the same ratio. Moreover, both oxygen and

TABLE 7. *Occlusion of oxygen and argon at −183° and 76 cm. pressure in porous glass and Doucil containing nitric oxide.*

	Porous glass	"Doucil"
Vol. of NO sorbed	19·49	26·28
Vol. of O_2 sorbed	31·3	82·5
Vol. of O_2 sorbed in absence of NO	42·4	96·8
Vol. of A sorbed	25·9	53·1
Vol. of A sorbed in absence of NO	35·1	62·7
Decrease in O_2 sorption, %	26·2	13·9
Decrease in A sorption, %	26·2	15·3

* All volumes are in terms of cm.³ (at S.T.P.)/g.

argon sorptions were reversible, as is illustrated for porous glass in Fig. 5*d*. It can be concluded with both porous glass and Doucil that reaction between sorbed nitric oxide and oxygen is inappreciable at −183°. It has been shown (*loc. cit.*) that nitric oxide sorbed in either of these gels does not disproportionate at −183°, so that lack of reactivity is here associated either with loss of free-radical character of the nitric oxide on sorption or else the low temperature.

DISCUSSION

The gas-phase oxidation of nitric oxide has a negative temperature coefficient and has been studied down to −192° (Briner, Pfeiffer, and Malet, *loc. cit.*), so that the lack of reactivity of oxygen towards nitric oxide occluded in several sorbents is of considerable interest. Both Szego and Guacci (*Gazzetta*, 1931, **61**, 333) and Briner and Sguaitamatti (*Helv. Chim. Acta*, 1941, **24**, 421) found that oxidation of nitric oxide occurred in silica gel. Their results were obtained by using a streaming method in which nitrous gases diluted with air traversed the bed of silica gel. They are accordingly not fully comparable with those in the present paper in which nitric oxide was sorbed first and in which the sorbed nitric oxide exerted no gas pressure. The steps proposed by Briner and Sguaitamatti for oxidation are: adsorption of nitric oxide and oxygen; reaction to form nitrogen dioxide (catalysed by the gel); adsorption of nitrogen dioxide and dinitrogen trioxide. However, our demonstration that sorbed nitric oxide failed to react with subsequently sorbed oxygen may require a modification of this mechanism. Briner and Boubnoff (*J. Chim. phys.*, 1913, **11**, 597) also considered that the disproportionation involved the stage $4NO = 2N_2O + O_2$, and that nitrogen dioxide resulted by oxidation of adsorbed nitric oxide. This mechanism for the same reason may also need reconsideration.

According to the free energies of formation of the species involved (nitric oxide, nitrous oxide, and dinitrogen trioxide) disproportionation of nitric oxide should go virtually to completion. Reaction less than 100% must therefore represent a non-equilibrium state. Briner and Boubnoff (*loc. cit.*) and Briner, Biedermann, and Rotken (*ibid.*, 1926, **23**, 157) have demonstrated that disproportionation of nitric oxide is already excessively slow in the gas phase at room temperature. Compression or liquefaction of nitric oxide was considered to favour reaction, although we have been unable to detect any reaction in *solid* nitric oxide at −183° in 100 hr. However, nothing comparable with the rapid catalyses reported in this paper has hitherto been reported. There are also striking differences between the zeolites acting as disproportionation catalysts and the relatively feeble catalyses observed with siliceous gel sorbents. Evidently the intracrystalline environment of the zeolites, perhaps on account of the polar surroundings and comparatively intense fields of force within the crystals, is especially favourable in promoting reactivity. By contrast with nitric oxide, nitrous oxide remains unactivated by the intracrystalline field for sorption temperatures up to 350°. The very ready activation of nitric oxide is therefore likely to be connected with its free-radical character.

The sorption of nitrous oxide in chabazite was studied by Lamb and Ohl (*J. Amer. Chem. Soc.*, 1935, **57**, 2154), who determined a calorimetric sorption heat of 12,830 cal./mole, to be compared with the isosteric differential heats of Table 1. Seeliger's data (*Physikal. Z.*, 1921, **22**, 563) for sorption of nitric oxide in chabazite give evidence of irreversible phenomena, but no detailed comparisons with our results are possible.

Finally, it may be noted that at 0° and room temperature the chabazite–nitric oxide system was yellow, but at −183° it was violet. A similar colour sequence was found with the other zeolites and with Doucil and porous glass. A reddish hue at −78° and black at −183° has been reported for nitric oxide–silica gel, but these colours were regarded as having a physical origin and as being due to a fine dispersion of capillary condensate (Briner and Sguaitamatti, *loc. cit.*). However, the colours observed in chabazite cannot be of this kind since the interstitial channels in this mineral are not wide enough for capillary-condensed sorbate to appear. No colours were observed in our experiments with nitric oxide–silica gel.

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Aliphatic Hydroxylamines. Part I. Preparation.

By M. A. THOROLD ROGERS.

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Methods for the preparation of *NN*-dialkylhydroxylamines from the corresponding amine are reviewed. The pyrolysis of tertiary amine oxides bearing at least one ethyl or propyl radical is a satisfactory, if occasionally ambiguous, method. *N*-Oxides of β-dialkylaminopropionic esters or nitrile, or of Mannich bases, decompose very readily to give the desired compound unambiguously.

IN this series of papers we shall be primarily concerned with *NN*-dialkylhydroxylamines, $(R{\cdot}CH_2)_2N{\cdot}OH$. No new methods for the preparation of the monoalkylhydroxylamines are reported, but in later papers some of the properties of the monoalkylhydroxylamines will be compared with those of the dialkyl series. The cyclic hydroxylamines, *e.g.*, *N*-hydroxypiperidine, are regarded as dialkyl derivatives of hydroxylamine. Methods of preparation which use as starting material any substance other than the corresponding amine have not been considered, because they are not applicable to cyclic hydroxylamines. In fact, methods using, *e.g.*, nitroparaffins, although convenient for some monoalkylhydroxylamines, are not particularly convenient for the dialkyl series.

A number of methods for preparation of dialkylhydroxylamines from the corresponding amines has been reported; broadly, these fall into three groups.

(1) Direct oxidation of the secondary amine by hydrogen peroxide (Mamlock and Wolffenstein, *Ber.*, 1900, **33**, 159; Henry and Dehn, *J. Amer. Chem. Soc.*, 1950, **72**, 2780). This has been found to be quite unreliable, not surprisingly in view of the strong reducing properties of the hydroxylamines which are formed in the presence of hydrogen peroxide.

(2) Decomposition of certain types of amine oxides. In the simplest examples, Mamlock and Wolffenstein (*loc. cit.*) made dipropylhydroxylamine by liquid-phase pyrolysis of tripropylamine oxide, and Wenick and Wolffenstein (*Ber.*, 1898, **31**, 1560; cf. Haase and Wolffenstein, *Ber.*, 1904, **37**, 3228) prepared *N*-hydroxypiperidine by the pyrolysis of *N*-ethylpiperidine oxide. These results, which appear to have been overlooked by later workers (but cf. Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., 1929, p. 671), are fully confirmed and extended in this paper.

Cope, Foster, and Towle (*J. Amer. Chem. Soc.*, 1949, **71**, 3929, 3423) have studied the vapour-phase pyrolysis of 1- and 2-phenylethyl-*tert.*-amine oxides, and claim good yields in certain cases. The intermediates are not particularly easy to make, however, and the process has no particular advantage as a preparative method. Cope, Pike, and Spencer recently (*ibid.*, 1953, **75**, 3212) have made oxides of dimethylamino-*cyclo*octane, -*cyclo*heptane, and -*cyclo*hexane. These are degraded smoothly, giving high yields of the olefin and of dimethylhydroxylamine.

(3) Gambarjan and Kazaryan (*J. Gen. Chem. U.S.S.R.*, 1933, **3**, 222) and Gambarjan (*Ber.*, 1925, **58**, 1775) treated benzoyl peroxide with secondary amines and obtained *O*-benzoyldialkylhydroxylamines. The yields claimed could not be substantiated.

Pyrolysis of the amine oxides with loss of ethylene or propylene, now studied in some detail, is of general application and is the method of choice, but a limitation is the ambiguity of the elimination; it cannot be predicted with certainty that, *e.g.*, $Et_2PrN\rightarrow O$ will give $EtPrN{\cdot}OH + C_2H_4$ and not $Et_2N{\cdot}OH + CH_3{\cdot}CH{:}CH_2$ or both. By analogy with the Hofmann degradation of quaternary ammonium compounds, ethylene should be eliminated preferentially (Hanhart and Ingold, *J.*, 1929, 998). Cope, Foster, and Towle (*loc. cit.*), however, present evidence that an intra-molecular, cyclic process is involved, and that on occasion the stereochemistry of the olefin differs from that obtained by Hofmann degradation, so that the analogy is not good.

An alternative and unambiguous method has been developed for the preparation of secondary hydroxylamines from the corresponding amines under mild conditions. Compounds of the type $R_2N{\cdot}CH_2{\cdot}CH_2X$ ($X = CO_2R'$, CN, or COPh) react with monoperphthalic acid in ether, precipitating the phthalate of the *N*-oxide, $R_2N(\rightarrow O){\cdot}CH_2{\cdot}CH_2X,C_6H_4(CO_2H)_2$ (cf. Witkop and Kissman, *J. Amer. Chem. Soc.*, 1953, **75**, 1977, footnote, for evidence of the competing deoxygenation of the oxide by the per-acid). Most of the products are oily, but one was crystalline and gave a satisfactory analysis. They are unstable under alkaline conditions, and undergo a reverse Michael addition, the activation by the *N*-oxide being reminiscent of the well-known effect of quaternisation on Mannich bases. In a single experiment using perbenzoic acid in chloroform in place of perphthalic acid in ether, the secondary amine used being piperidine, the *N*-oxide benzoate was not precipitated, and the successful isolation of *N*-hydroxypiperidine shows that the reverse Michael reaction proceeded even more readily and without added alkali; possibly the alkalinity of the reaction mixture before 1 mol. of perbenzoic acid had been added was sufficient, but if free hydroxylamine was present at this stage it is remarkable that it should have survived admixture with further per-acid.

Extensions of both these methods are under investigation.

Experimental

A valuable spot test for hydroxylamines unsubstituted on the oxygen is provided by triphenyltetrazolium chloride which, in the presence of alkali, gives the characteristic purple-red colour of the reduction product. Snow (*J.*, 1954, 2588) has commented on the specificity of the reaction, and by its means the presence or absence of hydroxylamines can usually be safely deduced. The progress of ether-extractions, steam-distillation, and so on can be followed in this way.

Tertiary Amine Oxides.—The tertiary amine (1 mol.), hydrogen peroxide (1·1 mols.), and sufficient water, alcohol, or acetone to give a homogeneous mixture are mixed and heated under reflux (bath) at 50—60° until the starch–iodide test for hydrogen peroxide is negative (overnight). Lower homologues may react violently with hydrogen peroxide; the mixing should then be carried out with ice-cooling, and the mixture be kept for some hours in ice before being heated. Occasionally, the temperature requires to be raised to 70° for a further 24 hr. The solvent is removed under reduced pressure, and the thermal degradation is carried out without further purification of the oxide, which is usually obtained as a syrup. Methods for following the disappearance of amine and for decomposing the excess of hydrogen peroxide have been described by Cope, Foster, and Towle (*loc. cit.*).

Pyrolysis: General Method.—The syrup from the oxidation is heated, usually under reduced pressure, in an apparatus set up for distillation, with an efficient condenser and, for the lower homologues, ice-cooling of the receiver. The oil-bath temperature is raised slowly to about 130°; there is always a little dark residue. The distillate may be (*a*) treated with excess of oxalic acid, and the oxalate isolated, or (*b*) dried (KOH) and redistilled. Yields are rather variable, and those quoted are not necessarily maximal; for example, Cope, Foster, and Towle (*loc. cit.*), using a liquid-air trap and conducting the pyrolyses at low pressures, obtained over 90% yields of dimethylhydroxylamine from *NN*-dimethyl*cyclo*hexylamine oxide. There is usually a little tar remaining from the pyrolysis. It is often convenient, when working on a

large scale, to conduct the pyrolysis under reflux, with adequate precautions for disposal of the large volumes of ethylene or propylene evolved, at atmospheric pressure, and then to distil the product under reduced pressure.

NN-Dimethylhydroxylamine is most conveniently made by pyrolysing the concentrated aqueous solution of the *N*-oxide of *NN*-dimethyl*cyclo*hexylamine in a glass tube packed with glass or porcelain rings, heated electrically to 200—220°, in a slow stream of nitrogen. Molar quantities can be handled very well in this way with satisfactory yield. The batchwise pyrolysis of the *N*-oxide of dimethyl*cyclo*hexylamine is liable to be violent, and the anhydrous *N*-oxide sublimes into the condenser.

β-Dimethylaminopropiophenone Oxide Phthalate.—The base made from β-dimethylaminopropiophenone hydrochloride (90 g.) in ether (about 200 c.c.) was stirred, with external ice-cooling. Monoperphthalic acid (*Org. Synth.*, 1948, **20**, 70 [a]) (750 c.c., 1 mol. in 2·2 l.) was run in at such a rate that the temperature remained below 15°. A transient pale blue colour appeared during the addition, and a mobile oil separated. Addition of the acid solution was stopped when the ethereal layer showed a permanent positive starch–iodide reaction

Pyrolysis of amine oxides.

Amine oxide	Hydroxylamine produced	B. p.	Yield (%)	Notes
$PrMe_2NO$	$Me_2N{\cdot}OH$	—	20	$Me_2N{\cdot}OH$ is very volatile. The pyrolysis was conducted at atmospheric pressure, and the receiver, which was cooled in ice, contained water.
$C_6H_{11}{\cdot}NMe_2O$ ...	$Me_2N{\cdot}OH$	—	61	Pyrolysed through hot tube. See above.
Et_2NO	$Et_2N{\cdot}OH$	50°/17 mm.	67	
$Pr^n{}_2NO$	$Pr^n{}_2N{\cdot}OH$	70°/17 mm.	50—79	
$Pr^n{}_2MeNO$	$Pr^nMeN{\cdot}OH$	98—99° (*ca.*)	—	Some material was lost. Isolated as *hydrogen oxalate*,[a] m. p. 112—113° from acetone.
Et_2MeNO	$EtMeN{\cdot}OH$	26—30°/10 mm.	82	*Hydrogen oxalate*,[b] m. p. 112—113° from acetone.
$[CH_2]_5{>}NEtO$	$[CH_2]_5{>}N{\cdot}OH$	89°/23 mm.	42	Yield based on *hydrogen oxalate*[c] (m. p. 112°, from methanol), isolated from primary distillate by evaporation with aqueous oxalic acid.

[a] Found: C, 40·4; H, 7·2; N, 8·0. $C_6H_{13}O_5N$ requires C, 40·2; H, 7·3; N, 7·8%. [b] Found: C, 36·4; H, 6·9; N, 8·6. $C_5H_{11}O_5N$ requires C, 36·35; H, 6·7; N, 8·5%. [c] Found: N, 7·2. $C_7H_{13}O_5N$ requires N, 7·3%.

(5 min.). The ether was removed by decantation, and the oil rinsed with ether two or three times. To the residue was added 2N-sodium hydroxide (300 c.c.), and the whole was distilled under reduced pressure with use of an efficient condenser system and ice-cooled receiver, until the distillate no longer showed reducing properties. Excess of aqueous oxalic acid was added to the distillate, which was then evaporated to dryness, and the hydrogen oxalate crystallised from methanol; it had m. p. 146—148° (12·73 g., 21·5%).

Ethyl β-Dialkylaminopropionate N-Oxide Phthalates.—β-Disubstituted aminopropionic esters (Whitmore, Masher, Adams, Taylor, Chaplin, Weisel, and Yanke, *J. Amer. Chem. Soc.*, 1944, **66**, 725), dissolved in a little ether, were treated with monoperphthalic acid. (Cooling is convenient, as the ether is liable to boil, but has little effect on the yield.) The phthalates of the following oxides were obtained as oils, and not isolated or characterised: ethyl β-diethylaminopropionate *N*-oxide; ethyl β-di-*n*-propylaminopropionate *N*-oxide; ethyl β-di-*n*-butylaminopropionate *N*-oxide; ethyl β-piperidinopropionate *N*-oxide. *Ethyl β-morpholinopropionate N-oxide phthalate* crystallised, and was isolated as white needles (83%), m. p. 129—130°, from alcohol (Found: C, 54·9; H, 6·0; N, 4·1. $C_{17}H_{23}O_8N$ requires C, 55·3; H, 6·3; N, 3·8%).

Ethyl β-piperidinopropionate *N*-oxide benzoate was made (also as an oil) by the use of perbenzoic in place of monoperphthalic acid (see below).

Decomposition of the N-Oxide Salts.—No standard procedure could be devised. The hydroxylamines were prepared in the following ways:

NN-*Diethylhydroxylamine.* The *N*-oxide phthalate from 61 g. of ethyl β-diethylamino-

[a] The process as described was liable to lead to vigorous decomposition during the preparation. Addition of 0·5% of quinol to the phthalic anhydride prevented this.

propionate was dissolved in acetone (200 c.c.) and stirred with solid anhydrous potassium carbonate until effervescence ceased and was not resumed on addition of more potassium carbonate. The solution was filtered and made acid (Congo-red) with an acetone solution of anhydrous oxalic acid. There was no precipitate, so the solution was evaporated to dryness and the gummy residue was extracted with ethyl acetate repeatedly until the residue was no longer reducing. The *hydrogen oxalate* (30 g.) separated as slightly sticky crystals, which, recrystallised from acetone, had m. p. 106—107° (Found: C, 40·6; H, 7·5; N, 7·8. $C_6H_{13}O_5N$ requires C, 40·2; H, 7·3; N, 7·8%). The yield is 50% based on the crude material. The neutral oxalate is recorded (Wieland, *Ber.*, 1903, **36**, 3216) as having m. p. 138°.

NN-*Dipropylhydroxylamine*. The *N*-oxide phthalate from ethyl β-dipropylaminopropionate (95 g.) was dissolved in acetone (250 c.c.) and stirred with excess of anhydrous potassium carbonate. The filtered solution was treated with excess of a solution of anhydrous oxalic acid in acetone. The hydrogen oxalate, m. p. 137—138°, was precipitated in 56% yield and could be recrystallised from acetone. In some preparations the material was contaminated with the oxalate of the starting material and careful fractionation was required. Alternatively, the *N*-oxide could be dissolved in aqueous alkali, and the hydroxylamine extracted with ether.

NN-*Dibutylhydroxylamine*. The oily *N*-oxide phthalate was dissolved in water and basified with potassium hydroxide. On cooling in ice the hydroxylamine solidified and was collected. The hydrogen oxalate, crystallised from water, had m. p. 140—141° (Dermer and Dermer, *J. Amer. Chem. Soc.*, 1942, **64**, 3057, give m. p. 144—144·5°).

N-*Hydroxymorpholine*. The *N*-oxide phthalate (59 g.) was heated with aqueous ammonia under reflux for 2 hr. The solution was evaporated to dryness, and the gummy residue extracted with hot acetone. The acetone was distilled, leaving an oil, which was distilled (7·76 g.; b. p. 66—66·9°/5 mm., n_D^{25} 1·4690) (Found: C, 46·4; H, 9·1; N, 13·4. Calc. for $C_4H_9O_2N$: C, 46·6; H, 8·8; N, 13·6%). It solidified in ice, and had m. p. 19—19·5°; it gave a *hydrochloride*, colourless prisms (from acetone), m. p. 103—105° (Found: C, 34·45; H, 8·05; N, 10·5. $C_4H_{10}O_2NCl$ requires C, 34·45; H, 7·15; N, 10·05%), and a *picrate*, needles (from toluene), m. p. 136° (Found: N, 16·8. $C_{10}H_{12}O_9N_4$ requires N, 16·9%).

N-*Hydroxypiperidine*.—Ethyl β-piperidinopropionate (26 g.) in chloroform (25 c.c.) was treated with a chloroform solution of perbenzoic acid until the mixture was peroxidic to starch–iodide paper. The *N*-oxide benzoate did not separate. The solution was evaporated to dryness, and the residue, dissolved in ether, gave, with anhydrous oxalic acid in acetone, a white precipitate, m. p. 104—106°, of the hydrogen oxalate of *N*-hydroxypiperidine.

2-*Cyanoethyldimethylamine*.—Into aqueous dimethylamine (24·8%; 1300 c.c.) was run acrylonitrile (212 g.) with external cooling to below 30° and stirring. The mixture was stirred for 1 hr. at room temperature, then for 1 hr. at 100°. Saturation of the cooled solution with sodium carbonate and extraction with ether gave the *base* (251·5 g.; b. p. 170°) (Found: N, 29·4%; *M*, by titration, 98. $C_5H_{10}N_2$ requires N, 28·6%; *M*, 98). The *picrate*, needles (from methanol–acetone), had m. p. 154—155° (Found: C, 40·7; H, 4·25. $C_{11}H_{12}O_9N_5$ requires C, 40·4; H, 4·0%).

2-*Cyanoethyldimethylamine Oxide Phthalate*.—To 2-cyanoethyldimethylamine (33 g.) in ether (100 c.c.) was added monoperphthalic acid in ether until the mixture showed a permanent positive starch–iodide reaction; a transparent oil separated, and this was collected by decantation and washed with ether. No solid derivative could be made. To decompose this *N*-oxide salt, the gum was dissolved in 2N-sodium hydroxide, and the mixture steam-distilled until the distillate was no longer reducing; the distillate was made slightly acid with aqueous oxalic acid, and the water removed under reduced pressure. The crystalline residue was extracted with methanol from considerable amounts of insoluble material, and from the extract on concentration there was obtained *NN*-dimethylhydroxylamine hydrogen oxalate (11·07 g., 22%), m. p. 148—149°.

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The Chemistry of Silica Surfaces.

By P. F. Holt and D. T. King.

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Solubility measurements indicate that an incomplete monolayer normally exists on silica surfaces which is more soluble than the rest of the material. This layer has been identified as silicic acid by following the exchange reaction between a quartz surface and dissolved [^{31}Si]silicic acid. The layer is removed by sodium hydroxide and re-formed when the silica is equilibrated with a silicic acid solution.

Lenher and Merrill (*J. Amer. Chem. Soc.*, 1917, **39**, 2630), using platinum apparatus, found that the solubility of gelatinous silica at 25° is 16·2 mg. and at 90° is 41·8 mg. of SiO_2 in 100 ml. of conductivity water. The solute was estimated gravimetrically. Equilibrium between the gelatinous silica and water was established after about 8 days at 25° and after 24 hours at 90°. Lenher and Merrill found that ignition of this silica reduced the rate of dissolution but concluded that " the true solubility of ignited silica is probably the same as that of gelatinous silica, but as saturation is not reached in any short period of time, the apparent solubility is somewhat less than that of the gelatinous silica." Alexander, Heston, and Iler (*J. Phys. Chem.*, 1954, **58**, 453) recently re-examined the values for the solubility of silica in water. Measuring the solute concentration by a colorimetric method, they found that amorphous silica produced by the combustion of silane, wet silica gel, and sols produced by treating sodium silicate with cation-exchange resins all had the solubility, 10—14 mg./100 ml. at 25°.

The values found for the solubility of quartz and other forms of silica are mostly much lower than Lenher and Merrill's values for silica gel; for example, Briscoe, Matthews, Holt, and Sanderson (*Trans. Inst. Min. Met.*, 1936—37, **46**, 291) found that, when 1 g. of quartz dust was shaken with 100 ml. of water at 20°, the solute contained only 1·6 mg. of SiO_2 per 100 ml. after 50 days. Other observers give widely differing values (see King and Belt, *Physiol. Rev.*, 1938, **18**, 329).

The rates of dissolution of various forms of silica have also been studied (see, *e.g.*, Briscoe, Holt, Matthews, and Sanderson, *loc. cit.*; Lucas and Dolan, *Canad. Med. Assoc. J.*, 1939, **40**, 127). It is generally agreed that, when powdered silica is added to water and the concentration of the dissolved silica is plotted against time, the curve shows an initial phase of rapid dissolution after which the silica dissolves much more slowly. If the extraction is continued for a number of days, in which saturation would be assumed, the concentration of the dissolved silicic acid depends upon the mass of silica extracted and the size of the particles. This initial rapid dissolution was also demonstrated indirectly by Benton and Elton (*Trans. Faraday Soc.*, 1953, **49**, 1213), who, when measuring ionic absorption energies, noted a rapid increase in the conductivity on adding powdered silica to water.

Kitto and Patterson (*J. Ind. Hyg. Toxicol.*, 1942, **24**, 59) attributed the initial rapid solubility of quartz to the presence of surface imperfections and to a disturbance of the surface caused by abrasion, likening the surface to the Beilby layer found on polished metals. This theory has been adopted more recently by Clelland and Ritchie (*J. Appl. Chem.*, 1952, **2**, 42), who estimated that the layer was between 0·02 and 0·15 μ thick, and by Nagelschmidt, Gordon, and Griffin (*Nature*, 1952, **169**, 538). Heavens, however (*Acta Cryst.*, 1953, **6**, 571), obtained sharp Kikuchi patterns in electron-diffraction photographs of the surface of a freshly fractured and an acid-washed quartz crystal, proving the absence of any thick layer of non-crystalline material. It is difficult to reconcile the fact that the abnormal solubility phenomena are shown by powdered fused silica with a theory which postulates organized and disorganized layers.

Lucas and Dolan suggested that the initial rapid dissolution was due to trace impurities such as alkali metals. Rapid dissolution from sharp corners and protruding edges was also suggested as the cause (Jötten and Pfefferkorn, *Arch. Hyg.*, 1953, **137**, 79). These theories are improbable, however, since it has been established that powders may still

show the unusual solubility characteristics after repeated extraction with water. A microscopic examination of some samples used for solubility determinations revealed insufficient small particles to account for the mass which dissolved rapidly.

We have sought further evidence to explain the anomalous solubility characteristics of silica by studying the rate of dissolution of powders and the effect of these powders on silicic acid solutions, and by observing the exchange phenomena which occur between solid silica and radioactive silicic acid sols.

Study of the process is complicated by polymerization of the dissolved silicic acid, which occurs most rapidly at pH 5·5—6 (Treadwell, *Trans. Faraday Soc.*, 1935, **31**, 298). Polymerization is much slower in more alkaline or more acid solutions. Our experiments were made primarily at high pH values at which polymerization was negligible. In most experiments buffers were not used since those acting over the alkaline pH range all interfere with the silicomolybdate reaction, the basis of the only colorimetric methods available for the estimation of silicic acid in low concentrations. Borate and acetate buffers were used for some experiments.

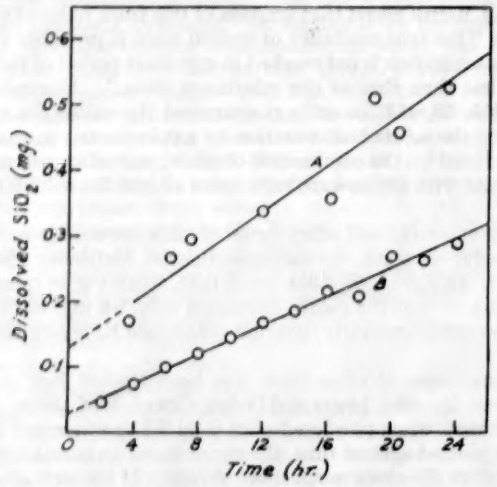

FIG. 1. *Rate of dissolution of silica powder in* 0·1N*-sodium hydroxide.*
(*A*) Original powder.
(*B*) Alkali-extracted powder.

Earlier workers emphasized a relation between particle size and mass (*i.e.*, surface area) of the silica powders and their rate of dissolution. Surface areas of all the powders were measured both by the method of projected areas and by nitrogen adsorption. On the silica powders used, these two methods gave values which differed by a factor of about 4. The values given by the nitrogen-adsorption method are probably more relevant. The silica powders were graded in size by water elutriation so that very small particles should not unduly affect the rate of dissolution. "Polythene" apparatus was used to prevent contamination of the solutions by silica derived from glassware.

Solubility–Time Curve of Silica Powders.—The rate of dissolution of a silica powder (2 g.) in 0·1N-sodium hydroxide (15 ml.) is shown in Fig. 1, curve *A*. Initially, dissolution is rapid but later is slow, the concentration–time plot being linear. Linear extrapolation of the curve shows that the mass of silica which dissolves rapidly is 0·13 mg. of SiO_2 per g. of powder.

The powder from this extraction was separated centrifugally, washed free from alkali, then dried at 120°. The rate of dissolution of this sample in 0·1N-sodium hydroxide is shown in Fig. 1, curve *B*, which lies below the previous curve, and, by extrapolation, the mass of silica which dissolves rapidly is only 0·03 mg. of SiO_2 per g. of powder.

These observations suggest that on the surface of the silica there is material which is easily dissolved, and from solubility and surface-area measurements obtained on two samples it is possible to estimate the extent of this layer, assuming that it is silicic acid and

is present as a monolayer. To calculate the values given in Table 1, an area of 12·3 Å^2 has been assumed for the silica unit. The measurements of surface areas made by nitrogen adsorption suggest that about one-sixth of the surface is covered.

TABLE 1.

Powder	Wt. of layer (mg./g.)	Surface area (m.^{2}/g.) (*a*) Optical	(*b*) N_2 adsorption	Fraction of surface covered by monolayer, calculated from : (*a*)	(*b*)
A	0·10	0·22	0·9	0·56	0·14
B	0·13	0·26	1·0	0·62	0·16

Adsorption of Silicic Acid on Silica Surfaces.—Further evidence for the presence of the surface layer was obtained by studying the effects of silica powders on silicic acid solutions. A silicic acid solution was prepared containing 10 mg. of SiO_2 in 100 ml. of solution in borate buffer, at pH 8, this concentration being well below that of a saturated solution as determined by Lenher and Merrill (*loc. cit.*) and equal to the lowest experimental value given by Alexander, Heston, and Iler (*loc. cit.*). A sample of the original silica powder was placed in this solution, and an equal weight of the alkali-extracted powder was placed in a similar volume of the same solution. The effect of the two powders on the concentrations of the silicic acid solutions is shown in Fig. 2. The original powder produced only a very small change in the concentration of the silicic acid solution (curve *A*) but the alkali-extracted powder adsorbed 0·12 mg. of SiO_2 from 100 ml. of solution. This result suggests that the

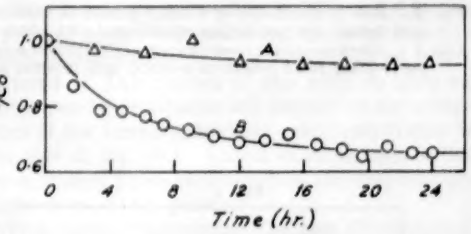

FIG. 2. *Adsorption of silicic acid from solution on to the original silica powder (curve A) and on to the alkali-extracted powder (curve B). The change in the concentration of the solute is denoted as the ratio of the concentration (c) after a measured time to the initial concentration (c_0).*

layer present on a silica surface which is removed by alkali is adsorbed silicic acid, and that the layer is re-formed when an alkali-washed silica surface is treated with a silicic acid solution.

The silica powder was recovered from the last experiment and its solubility in 0·1N-sodium hydroxide was followed. The rate curve is shown in Fig. 3. The later portion is approximately linear, and linear extrapolation shows that the mass of silica which dissolves rapidly from 1 g. of powder is almost identical with that adsorbed from the silicic acid solution. Moreover, the rate of solution after the adsorbed layer has been removed is almost identical with that of the alkali-washed material (Fig. 1). Calculations based on the surface area measured by nitrogen adsorption show that the adsorbed silicic acid, if present as a monolayer, covers a fraction of 0·16 of the silica surface.

Exchange between Adsorbed Silicic Acid and Dissolved Labelled Silicic Acid.—The results described suggest that surface adsorption occurs from silicic acid solutions on to silica surfaces. The adsorbed silicic acid may be able to exchange with dissolved silicic acid. The original silica powder (6 g.) and the alkali-extracted powder (6 g.) were placed in solutions of radioactive silicic acid (8 ml.). The changes in the total concentration of dissolved silicic acid, measured colorimetrically, and in the concentration of the radioactive silicic acid, were followed. This experiment was performed at several pH values. When the original silica powder was added to a radioactive silicic acid solution at pH 8 or at pH 9 the concentration of the dissolved ^{31}Si fell, equilibrium being established after about 4 hours (Fig. 4, curve *A*). The total concentration of dissolved silicic acid, measured colorimetrically, remained approximately constant (Fig. 4, curve *B*). When the experiments were carried out at pH 4 or pH 5 the concentrations of both the ^{31}Si and the molybdate-reactive silicic acid remained constant. Fig. 5 shows the results obtained at pH 4. Ex-

change can occur, then, in alkaline but not in acid solutions, suggesting that only the silicate ion can take part in the exchange reaction.

An alkali-extracted silica powder (2 g.) adsorbed silicic acid from a solution (8 ml.) at pH 8. In this case the reduction in the concentration as shown colorimetrically was identical with the reduction indicated by the tracer technique, showing that adsorption had occurred (Fig. 6). When the alkali-extracted silica was treated with silicic acid solution at pH 8, the resulting powder would exchange with dissolved radioactive silicic acid. Thus, when 5 g. oft he alkali-extracted powder used in the last experiment were

FIG. 3.

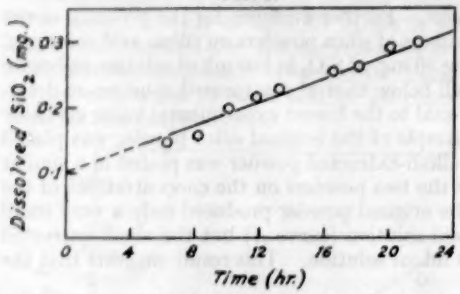

FIG. 4.

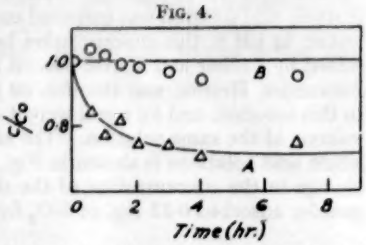

FIG. 3. *Rate of dissolution of a silica powder in* 0·1N-*sodium hydroxide. This powder was first extracted with sodium hydroxide then equilibrated with silicic acid solution before the solubility was followed.*

FIG. 4. *Alteration in the concentration of* [^{31}Si]*silicic acid (curve A) and total silicic acid (curve B) on adding the original silica powder to a silicic acid solution at* pH 8. *For c and* c_0, *see Fig.* 2.

FIG. 5.

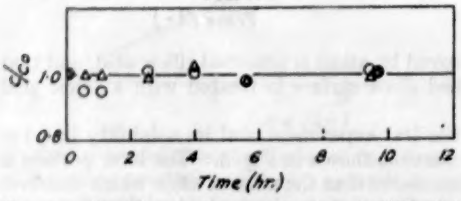

FIG. 6.

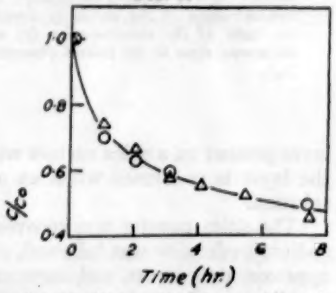

FIG. 5. *Alteration in the concentration of* [^{31}Si]*silicic acid* (Δ) *and total silicic acid* (○) *on adding the original silica powder to a silicic acid solution at* pH 4. *For c and* c_0, *see Fig.* 2.

FIG. 6. *Alteration in the concentration of* [^{31}Si]*silicic acid* (Δ) *and total silicic acid* (○) *on adding the alkali-extracted silica powder to a silicic acid solution at* pH 8. *For c and* c_0, *see Fig.* 2.

equilibrated with a silicic acid solution, then transferred to a solution of isotopically-labelled silicic acid, the ratio of the final to the initial concentration of dissolved silicic acid increased slightly to 1·1 during 8 hr. but the ratio as measured by the tracer technique fell to 0·61. This indicates that there was 0·12 mg. of SiO_2 per g. of powder which would exchange with dissolved silicic acid, a value very close to that found for the original powder.

These results show that silica surfaces will adsorb silicic acid and that the adsorbed layer is identical with the " high solubility layer " which has been widely investigated. The layer is removed by alkali and is re-formed by adsorption from silicic acid solutions even if the concentration is well below that of a saturated solution. The published solubility–time curves of quartz may be dissected into two portions. The first, the " high solubility phase," is due to the dissolution of the adsorbed silicic acid layer, and the second portion represents the attack of water on the true silica lattice. The latter is very slow and the rate depends largely on the pH; preliminary results indicate that the rate at pH 14 is approximately 100 times that at pH 4.

When silica powder is added to water, any adsorbed silicic acid will dissolve rapidly at first until the rate of dissolution becomes equal to the rate of adsorption. An equilibrium will not be established in any short time unless the mass of adsorbed silicic acid is sufficient to saturate the solution: thus Alexander, Heston, and Iler (*loc. cit.*), when determining the solubility of a very finely divided amorphous silica, found that the "solubility of this silica was relatively independent of the mass, *except when less than* 0·1% *silica powder is present* in the dispersion." If it is assumed that the proportion of the surface covered by adsorbed silicic acid was the same as for our samples, the mass of silica in the adsorbed layer can be calculated from the given surface area (B.E.T.) values to be approximately 31 mg. of SiO_2 per g. of powder. The adsorbed silicic acid on 0·1 g. of the powder would then be 3·1 mg., representing a solution concentration of 3·1 mg. of SiO_2 per 100 ml., a lower value than the total solubility found by Alexander *et al.* (10—14 mg./100 ml.) but, in view of the assumptions made, a value of the right order. The powder, produced by combustion of silane, had an extremely small particle size and it was extracted for 20 days. The dissolution of silica from the lattice may have contributed appreciably, therefore, to the measured solubility.

It is apparent that the amount of silica which passes rapidly into solution in this way will depend on the surface area presented by the powder and also on its previous history. The measurements of "solubility" previously made at pH values near neutrality will represent mainly the extent of the adsorbed silicic acid layer on the surface of the particular silica powder which was used. There is, then, no justification for the statement (Alexander, Heston, and Iler, *loc. cit.*) "it is well known that amorphous silica is more soluble than crystalline silica (quartz)." The equilibration of quartz with water has never been accomplished, at least at neutrality and at normal temperatures. The dissolution of quartz requires the attack of water on the silica lattice. The kinetics of this reaction have not been studied at normal temperatures, and the rate of dissolution will depend on the surface area of the sample of quartz, but some idea of the time required for equilibration may be obtained from the curve published by Briscoe *et al.* (*loc. cit.*). Linear extrapolation of that part of the curve which represents the slow solubility phase indicates that the time required for equilibration in this case is considerably in excess of ten years.

In a number of communications both the curves representing the rate of solution of silica powders and the particle diameters were given. If it is assumed that the fraction of the surface covered by the silicic acid monolayer was the same in these dusts as in ours, it is possible to calculate the specific surface of the dust from the mass of silica which dissolved rapidly. These values may be converted into average particle diameters by assuming that the surface area–particle diameter relation is the same in all the powders and measuring this relation for a silica powder. The observed and calculated diameters are set out in Table 2. The divergence between the calculated and the observed values increases as the

TABLE 2.

	Particle diameter (μ)			Particle diameter (μ)	
Author *	Obs.	Calc. from hydrated layer theory	Author *	Obs.	Calc. from hydrated layer theory
1	1—3	1	5	0·2—0·5	0·13
2	1—3	0·25		0·33	0·13
3	5—7	2·6		0·27	0·09
	0·5—3	0·3		0·27	0·06
4	2—5	2		0·25	0·03
	0·02—0·06	0·02	6	50—200	95

* (1) Briscoe, Holt, and Sanderson, *loc. cit.* (2) King and McGeorge, *Biochem. J.*, 1938, **32**, 417. (3) Lucas and Dolan, *loc. cit.* (4) King, *Occup. Med.*, 1947, **4**, 26. (5) Kitto and Patterson, *loc. cit.* (6) Clelland, Cumming, and Ritchie, *J. Appl. Chem.*, 1952, **2**, 31.

particle size decreases. This is probably due to uncertainty in the optical estimation of the diameter of very small particles. According to our results, these samples must have contained particles which were below the limit of resolution of the optical microscope.

In view of these results, much of the work which has been carried out on silica surfaces would bear re-examination and re-interpretation. A surface can be regarded as silica only

if it has been pre-treated with alkali. Even then, some degree of dissolution of silica and readsorption of silicic acid may occur if the sample is dried. When powders are not pre-treated, the observed properties are those of a mixed surface of silica and silicic acid.

The polymerization of silicic acid is usually regarded as a process of condensation: "All silica and silicate structures are derived by linking SiO_4 tetrahedra . . . similar principles should be applied to the constitution of colloidal silica" (Carman, *Trans. Faraday Soc.*, 1940, **36**, 964); however, Weyl and Hauser (*Kolloid Z.*, 1951, **124**, 72), emphasizing that silicon has a marked tendency to expand its outer shell to 12 electrons by co-ordination, suggested that orthosilicic acid has the structure $H_2Si(OH)_6$, and that its polymerization is due to the aggregation of these units to form a macromolecule in which each silicon atom has a co-ordination number of 6. They represent condensation as a second stage in the polymerization.

There is little doubt that the surfaces of silica particles are normally covered by hydroxyl groups (Shapiro and Weiss, *J. Phys. Chem.*, 1953, **57**, 219). The adsorption of silicic acid on to a silica surface is, then, analogous to the first stage of the polymerization of silicic acid. We have shown, however, that dissolved silicic acid will not exchange with a silica lattice but will exchange with adsorbed silicic acid; it follows that the linkage between the silicon atoms in the surface and those of the adsorbed layer is different from the linkage between silicon atoms in the lattice. This precludes the formation of Si–O–Si linkages between the adsorbed silicic acid and the quartz surface. It is therefore improbable that this type of linking exists in the polysilicic acids, sols, and gels.

Our results, then, support Weyl and Hauser's conception that the polymerization of silicic acid is by co-ordination, but suggest that the second stage, the condensation, never occurs unless the polysilicic acid is heated, for example, under such conditions as are used for growing quartz crystals. "Gelatinous silica" and all polysilicic acids are, then, a mass of co-ordinated orthosilicic acid molecules. This view accords with many of the observed properties of polysilicic acids; indeed, on the condensation theory of polymerization, it is difficult to explain why ignited silica gel is a dehydrating agent.

Our observations neither prove nor disprove the presence of a thick disorganized layer on the surface of silica particles. They do suggest, however, that the anomalous solubility phenomena which have been reported are not due to such a layer.

Experimental

Reagents.—Quartz powder. Pure rock crystal (supplied by Hilger & Watts, Ltd.; 99·8% SiO_2) was finely powdered and a fraction containing particles of size 5—15 μ (measured microscopically) was separated by repeated sedimentation of the powder in water. A dispersion of the fraction in aqueous ethanol or sodium oxalate was set aside for some minutes and the liquid layer was transferred to the cell of a photoelectric colorimeter. A negligible galvanometer reading was produced, indicating that fine particles were virtually absent. The powder was air-dried in an oven at 120°.

Radioactive silica. Pure fused silica ("Vitreosil") in a sealed silica tube was irradiated in the Harwell pile (B.E.P.O.) for 12 hr. The isotope of mass 30 undergoes thermal neutron capture to give the β-emitter, ^{31}Si, with a half-life of 2·85 hr.

Silicate solutions. Pure fused silica ("Vitreosil") was fused with twice its weight of anhydrous sodium carbonate in a platinum crucible, and, after cooling, the melt was dissolved in water.

Apparatus.—The reaction vessels were 5" lengths of 5/8" diameter "Polythene" tubing, closed at each end by hard rubber bungs. The suspensions were continuously agitated by clipping the vessels to a horizontal rotating shaft making 60 r.p.m. The whole apparatus was immersed in a water thermostat at 25·00° ± 0·05°. The clear liquid was separated from the suspensions by centrifugation at 3000—4000 r.p.m.

Analytical Methods.—(1) *Colorimetric determination of silica.* The method used depends upon the formation and measurement of the coloured silicomolybdate complex (see King and Stantial, *Biochem. J.*, 1933, **27**, 990). The yellow colour was estimated in a single-cell colorimeter of the type described by Morris (*Brit. Med. J.*, 1944, **2**, 81), an Ilford Spectrum Violet 601 filter being used.

(2) *Isotopic assay of silica.* ^{31}Si is a fairly energetic β-emitter (1·8 Mev) and can be assayed, therefore, by liquid-counting methods. A Geiger–Muller counter described by Veall (*Brit. J. Radiol.*, 1948, **21**, 347) was used in conjunction with a power pack and scaler ("Dynatron" Nos. 200A and 1172A).

Measurements of Surface Area.—(1) *Optical method.* A photomicrograph was made of a random sample of powder and a calibrated graticule. Enlarged prints were prepared. The mean projected area was found by cutting out the photographs of the particles, weighing them, and comparing the weights with that of standard squares based on the photograph of the graticule. The surface area was calculated by assuming that the particles were cubes.

(2) *Nitrogen adsorption.* The standard B.E.T. procedure was used. The apparatus was kindly lent by Esso European Laboratories, Abingdon.

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Experiments on the Synthesis of the Pyrethrins. Part IX. The Addition of Ethyl Diazoacetate to Sorbic Esters.*

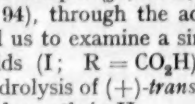
By STANLEY H. HARPER and HUGH W. B. REED.

[Reprint Order No. 5852.]

It is shown that ethyl diazoacetate adds predominantly to the γδ-ethylenic bond of methyl sorbate and α-methylsorbate to form the *cyclo*propane derivatives. From the adduct with methyl sorbate two crystalline isomeric 2-2′-carboxyvinyl-3-methyl*cyclo*propane-1-carboxylic acids are isolated, and their structures and configurations are established by degradation to isomeric 3-methyl*cyclo*propane-1 : 2-dicarboxylic acids.

This opens the way to a synthesis of chrysanthemumdicarboxylic acid, or a stereoisomer thereof, by the addition of ethyl diazoacetate to an ester of αδ-dimethylsorbic acid.

THE successful synthesis of the chrysanthemic acids (I; R = Me) developed by Campbell and Harper (*J.*, 1945, 283; cf. Harper, Reed and Thompson, *J. Sci. Food Agric.*, 1951, **2**, 94), through the addition of ethyl diazoacetate to 2 : 5-dimethylhexa-2 : 4-diene, has led us to examine a similar approach to the synthesis of the chrysanthemumdicarboxylic acids (I; R = CO_2H). A (+)-*trans*-chrysanthemumdicarboxylic acid arises from the hydrolysis of (+)-*trans*-pyrethric acid (I; R = CO_2Me), the acidic component of cinerin-II and pyrethrin-II.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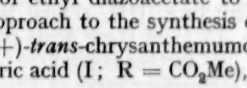
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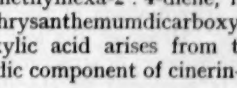

(III)

The olefinic component required would be an ester of the hitherto undescribed αδ-dimethylsorbic acid, and successful synthesis would necessitate addition at the γδ-ethylenic bond. To gain information on the latter point attention was directed, initially, to the addition of ethyl diazoacetate to esters of the readily accessible sorbic and α-methylsorbic acids.

As the mechanism of the "high-temperature" addition of aliphatic diazo-compounds to olefins remains uncertain, though with a bias in favour of the participation of free radicals, confident prediction of the influence of polar groups cannot be made. Existing evidence relating to dienes is scanty and conflicting. Heide (*Ber.*, 1904, **37**, 2101) showed that, with 1-phenylbutadiene, ethyl diazoacetate adds to the γδ-ethylenic bond. In contrast, Guha and Sankaran (*Ber.*, 1937, **70**, 2109) observed terminal addition of diazomethane to ethyl muconate. Of other additions probably proceeding by a free-radical mechanism, epoxidation of methyl sorbate by perbenzoic acid gives γδ-addition, as does peroxidation (Heinänen, *Suomen Kem.*, 1935, **8**, *B*, 5; 1938, **11**, *B*, 2). Hence it seemed

* Part VIII, *J.*, 1952, 869.

likely that γδ-addition of ethyl diazoacetate to simpler sorbic esters would predominate but the formation of several geometrical isomers owing to lack of symmetry, and of structural isomers owing to the non-identity of the ethylenic bonds, would render the isolation of pure individuals more difficult than in the case of the chrysanthemic acids.

Ethyl diazoacetate was added to methyl sorbate and to methyl α-methylsorbate in refluxing light petroleum (b. p. 100—120°) in the presence of copper bronze. Vigorous evolution of nitrogen occurred and subsequent distillation gave the adduct in 25—30% yield. Great difficulty was encountered in obtaining any crystalline products either after hydrolysis or on ozonolysis. First success was achieved with the adduct from methyl α-methylsorbate. Ozonolysis of this adduct gave, after decomposition, in the steam-distillate pyruvic acid, identified as the 2 : 4-dinitrophenylhydrazone and presumably derived from the intermediate methyl pyruvate by ready hydrolysis. From the portion involatile in steam a crystalline dibasic acid, m. p. 138°, of the formula $C_6H_8O_4$ was isolated and characterised by crystalline di-*p*-nitrobenzyl, di-*p*-bromophenacyl, and di-*p*-phenylphenacyl esters. This acid could be only a 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid and, therefore, derived from an adduct acid (II) formed by γδ-addition of ethyl diazoacetate. The isolation of pyruvic acid substantiated this conclusion. None of the products that would arise from the degradation of an adduct resulting from αβ- or αδ-addition was isolated.

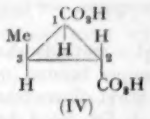
Attention was redirected then to the adduct from ethyl diazoacetate and methyl sorbate. On a larger scale the adduct was fractionally distilled and the fractions were separately hydrolysed to gummy acids which partially and slowly crystallised. Fractional crystallisation of the solid gave a less soluble acid, m. p. 184°, and a more soluble acid, m. p. 195°. Each acid was characterised as its di-*p*-nitrobenzyl and di-*p*-phenylphenacyl ester. These acids were isomeric, dibasic, and of the expected formula $C_8H_{10}O_4$. Furthermore, both showed a high-intensity absorption band at 229 mμ, indicative of the presence of $\cdot CH{:}CH\cdot CO_2H$. Ozonolysis of the acid, m. p. 195°, gave the same 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid, m. p. 138°, as was obtained from the methyl α-methylsorbate adduct; their identity was established by comparison of the di-*p*-nitrobenzyl, di-*p*-bromophenacyl, and di-*p*-phenylphenacyl esters. Ozonolysis of the acid, m. p. 184°, also gave a 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid, m. p. 135°, but characterisation of this acid as its di-*p*-nitrobenzyl and di-*p*-phenylphenacyl esters showed it to be not identical with the acid of m. p. 138°. The adduct acids, m. p.s 184° and 195°, therefore, are stereoisomers of the desired structure (III), arising from γδ-addition to the sorbic ester. However, the low yield (*ca.* 15%) of these acids points to the presence of other stereoisomers or structural isomers; no further crystalline products were obtained.

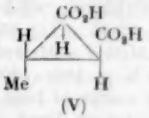
It remained to elucidate the stereochemistry of these "bisnor"-chrysanthemum-dicarboxylic acids by consideration of the identity of the two 3-methyl*cyclo*propane-1 : 2-dicarboxylic acids. Three optically inactive forms of the latter acids are possible, (IV)—(VI). Although the identification of these acids and the assignment of their configurations was a controversial issue of the 1920's, throughout the controversy no derivatives of these acids were prepared. The sole remaining criterion of identity is the melting points of the acids which, however, were shown to be markedly depressed by traces of moisture or solvent. If the configurations assigned by Goss, Ingold, and Thorpe (*J.*, 1923, **123**, 3342) are accepted, the *trans*-acid (IV) * has m. p. 195°, and is thus removed from further consideration. The *trans*-3 : *cis*-2-acid (V) was ascribed m. p. 132° by Goss, Ingold, and Thorpe (*loc. cit.*) but later (*idem*, *ibid.*, 1925, **127**, 460) was shown to be identical with the acid of m. p. 147° isolated by Feist (*Annalen*, 1924, **436**, 125; cf. Kon and Nanji, *J.*, 1932, 2557). The *cis*-*cis*-acid (VI), first obtained by Preisweck (*Ber.*, 1903, **36**, 1085), was ascribed the m. p. 108° (solvated form ?) and may be identical with a *cis*-acid, m. p. 94°, obtained by Feist (*loc. cit.*).

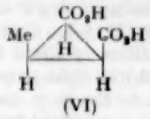
It was evident that mere inspection did not permit of identification. We repeated, therefore, Goss, Ingold, and Thorpe's synthesis which utilises the condensation of ethyl sodiomalonate with ethyl αβ-dibromobutyrate. In our hands, however, prolonged hydro-

* In this designation the CO_2H at position 1 is the reference group for both *cis*-2 and *trans*-3.

chloric acid hydrolysis of the intermediary triethyl *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylate gave no 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid but γ-methylparaconic acid, the product of fission of the *cyclo*propane ring. Brief acid hydrolysis gave *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid, better obtained by alkaline hydrolysis. Decarboxylation of the tricarboxylic acid was accompanied by the evolution of water, pointing to the preferential formation of the anhydride of (VI). Hydrolysis gave *cis*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (VI), which separated from benzene in a solvated form of indistinct melting point. Preparation of the di-*p*-nitrobenzyl and the

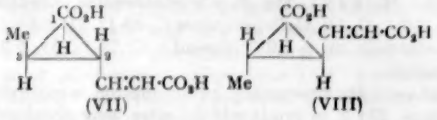

(IV)


(V)


(VI)

di-*p*-phenylphenacyl ester and comparison showed then to be identical with the derivatives of our acid (m. p. 135°) derived from the adduct acid, m. p. 184°.

Four isomeric 2-2′-carboxyvinyl-3-methyl*cyclo*propane-1-carboxylic acids could be formed from methyl *trans-trans*-sorbate, (VII) and (VIII) by addition without inversion and (IX) and (X) by addition with inversion (the carboxyvinyl group having the *trans*-configuration throughout). Of these, only (X) can give rise to (VI) on ozonolysis, which is therefore the configuration of the acid, m. p. 184°. By exclusion the 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid of m. p. 138° is the *trans*-3 : *cis*-2-isomer (V). Now of the remaining adduct acids (VII)—(IX), only (VIII) can give rise to (V) on ozonolysis, which is therefore the configuration of the adduct acid, m. p. 195°, from methyl sorbate (also of the acid present but not isolated in the adduct from methyl α-methylsorbate).


(VII) (VIII) (IX) (X)

That ordinary sorbic acid has the *trans-trans*-configuration is well established; the evidence has been summarised recently by Eisner, Elvidge, and Linstead (*J.*, 1953, 1372). These authors showed that partial inversion to *cis-trans* markedly affects the ultra-violet light absorption, the single high-intensity band (*e.g.*, for methyl sorbate, $\lambda_{max.}$ 258 mμ, ε 31,500) giving way to less intense absorption showing multiple bands. The configuration of the only known form of α-methylsorbic acid, prepared by the Reformatski reaction, has remained uncertain. We find that methyl α-methylsorbate shows the single high-intensity band ($\lambda_{max.}$ 263 mμ, ε 27,400) that would be expected for a *trans-trans*-configuration, with the additional methyl substituent producing a bathochromic shift of 5 mμ.

Addition of ethyl diazoacetate to the γδ-ethylenic bond of methyl sorbate has occurred both with and without inversion at one of the γ or the δ carbon atoms. Hence reaction does not proceed by a broadside approach of an ethoxycarbonylmethylene radical and simultaneous addition at both ends of the ethylenic bond. Addition of ethyl diazoacetate must be (at least) a two-stage process in which either a pyrazoline ring is formed and then broken or the ethoxycarbonylmethylene radical adds in two stages. Both would lead to a diradical intermediate which could retain or lose configuration at the free-radical carbon atoms. The course of the reaction would then parallel the photochemically catalysed addition of chlorine to olefins.

It has been generally assumed in additions of aliphatic diazo-compounds that the olefin retains its configuration, and configurations have been assigned on this basis. However, few additions have been studied by earlier workers in which inversion could have been unequivocally established. Only two other cases have been found, that of the addition of diazomethane to dimethyl *trans*-but-2-ene-2 : 3-dicarboxylate (von Auwers and König, *Annalen*, 1932, **496**, 252) and of diazo*iso*propane to ethyl maleate (Guha and Sankaran, *Ber.*, 1937, **70**, 1688).

Experimental

Ultra-violet light absorptions were determined in EtOH in a Unicam SP. 500 spectrophotometer by Mr. K. C. Sleep.

Sorbic acid, m. p. 133—134°, was prepared by the Reformatski method in 18% yield and better by the Knoevenagel method in 28—32% yield (cf. Allan and VanAllan, *Org. Synth.*, 1944, **24**, 92). Methyl sorbate had b. p. 72°/12 mm., n_D^{25} 1·4950, d_4^{25} 0·9605. α-Methylsorbic acid, m. p. 100°, was prepared exclusively by the Reformatski method (cf. von Auwers and Heyna, *Annalen*, **1923**, **434**, 157) in 25% yield. *Methyl α-methylsorbate*, prepared with methanolic sulphuric acid, had b. p. 86°/12 mm., n_D^{20} 1·5044; light absorption, see text (Found: C, 68·3; H, 8·7. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%).

Addition of Ethyl Diazoacetate to Methyl α-Methylsorbate.—Methyl α-methylsorbate (56 g., 0·4 mol.) in light petroleum (50 ml., b. p. 100—120°) containing copper bronze (0·5 g.) was heated to the b. p. under reflux, the source of heat removed, and ethyl diazoacetate (23 g., 0·2 mol.; prepared by the method of Harper, Reed, and Thompson, *J. Sci. Food Agric.*, 1951, **2**, 94) added slowly: a vigorous exothermic reaction with evolution of nitrogen ensued. Distillation gave the adduct ester, b. p. 122—128°/3 mm., in approx. 10% yield (on the ethyl diazoacetate). Hydrolysis with ethanolic potassium hydroxide yielded the adduct acid(s) as a gum which did not crystallise.

The adduct ester (5·0 g.) was treated with excess of ozone in chloroform at 0° and the ozonide treated with water and steam-distilled. Addition of 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid to the distillate gave a precipitate of pyruvic acid 2 : 4-dinitrophenylhydrazone (0·5 g.), m. p. and mixed m. p. 212°. Evaporation of the solution of the involatile product gave a gum that slowly and partially crystallised. Recrystallisation of the solid from ethyl acetate gave *trans*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·33 g.), m. p. 138° [Found: C, 50·5; H, 5·2%; equiv., 71·8, 72·2. Calc. for $C_4H_6(CO_2H)_2$: C, 50·0; H, 5·6%; equiv., 72·1]. By standard procedures the *di*-p-*nitrobenzyl*, plates (from ethanol), m. p. 129° (Found: C, 58·1; H, 4·5. $C_{20}H_{18}O_8N_2$ requires C, 58·0; H, 4·4%), the *di*-p-*bromophenacyl*, needles (from ethanol), m. p. 171° (Found: C, 48·9; H, 3·7. $C_{22}H_{18}O_6Br_2$ requires C, 49·1; H, 3·4%), and the *di*-p-*phenylphenacyl ester*, laths (from ethanol), m. p. 193° (Found: C, 76·7; H, 5·3. $C_{34}H_{28}O_6$ requires C, 76·7; H, 5·3%), were prepared.

Addition of Ethyl Diazoacetate to Methyl Sorbate.—By proceeding as for methyl α-methylsorbate and recycling the recovered methyl sorbate, 234 g. of crude adduct ester were obtained from 300 g. of methyl sorbate. This adduct ester was separated by fractional distillation into six fractions (24·0, 29·5, 20·2, 36·4, 65·1, and 40·0 g.) within the range of b. p. 138—151°/12 mm., having n_D^{25} rising from 1·469 to 1·479, d_4^{25} within the range 1·095—1·100 and $[R_L]_D$ rising from 53·8 to 54·8 (Calc.: 53·54). These fractions were separately hydrolysed with ethanolic potassium hydroxide, and the isolated gummy acids kept during several months during which slow partial crystallisation occurred. Trituration with ethyl acetate enabled the solids (0, 0·5, 4·8, 4·0, 6·4, and 9·5 g.) to be separated from the remaining gums. No further crystallisation occurred.

Separate crystallisation from ethyl acetate gave the same less soluble product, cis-2-(trans-2-*carboxyvinyl*)-cis-3-*methyl*cyclo*propane*-1-*carboxylic acid* (5·8 g.), m. p. 184°, $\lambda_{max.}$ 229 mμ (ε 17,600) [Found: C, 56·4, 56·5; H, 5·5, 5·8%; equiv., 85·0, 85·1. $C_6H_8(CO_2H)_2$ requires C, 56·5; H, 5·9%; equiv., 85·1]. The *di*-p-*nitrobenzyl ester* crystallised in plates, m. p. 134°, from ethanol (Found: C, 59·9; H, 4·6. $C_{22}H_{20}O_8N_2$ requires C, 60·0; H, 4·6%), and the *di*-p-*phenylphenacyl ester* crystallised from acetone–ethanol in plates, m. p. 164° (Found: C, 77·5; H, 5·4. $C_{36}H_{28}O_6$ requires C, 77·4; H, 5·4%).

Evaporation of the filtrates from the above acid and extraction of the residue with hot water yielded a second acid. Recrystallisation of this from ethyl acetate gave cis-2-(trans-2-*carboxyvinyl*)-trans-3-*methyl*cyclo*propane*-1-*carboxylic acid* (0·74 g.), m. p. 195°, $\lambda_{max.}$ 229 mμ (ε 19,400) (Found: C, 56·8; H, 5·5%; equiv., 85·6, 85·7). The *di*-p-*nitrobenzyl ester* crystallised from ethanol in prisms, m. p. 112° (Found: C, 60·3; H, 4·9%), and the *di*-p-*phenylphenacyl* ester crystallised from acetone–ethanol in granules, m. p. 153° (Found: C, 77·8; H, 5·7%).

Ozonisations.—The acid (0·5 g.), m. p. 184°, was treated with excess of ozone in chloroform at 0°. The solution was evaporated under reduced pressure, the residue warmed with water, and the aqueous solution evaporated. The resulting gum slowly crystallised and on recrystallisation from benzene gave *cis*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·21 g.), m. p. 135° [Found: C, 49·8; H, 5·6%; equiv., 73·0, 73·5. Calc. for $C_4H_6(CO_2H)_2$: C, 50·0; H, 5·6%; equiv., 72·1]. The *di*-p-*nitrobenzyl ester* crystallised from ethanol in plates, m. p. 135°

(Found: C, 58·1; H, 4·3. $C_{29}H_{18}O_8N_2$ requires C, 57·95; H, 4·4%), and the *di*-p-*phenylphenacyl ester* similarly, m. p. 175° (Found: C, 76·9; H, 5·3. $C_{54}H_{38}O_6$ requires C, 76·7; H, 5·3%).

The acid (0·25 g.), m. p. 195°, being insoluble in cold chloroform, was treated with excess of ozone at 0° in ethyl acetate–chloroform (2 : 3). Working up as above and crystallising from benzene gave *trans*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·1 g.) in solvated form, m. p. 95—105° with evolution of vapour, which at 100° in a vacuum crumbled to a powder, m. p. 138° (Found: equiv., 71·7, 73·7). The di-*p*-nitrobenzyl ester had m. p. and mixed m. p. 129° (Found: C, 57·7; H, 4·5%), the di-*p*-bromophenacyl ester, m. p. and mixed m. p. 171° (Found: C, 48·9; H, 3·2. Calc. for $C_{32}H_{18}O_6Br_2$: C, 49·1; H, 3·4%), and the di-*p*-phenylphenacyl ester, crystallised from acetone–ethanol, had m. p. and mixed m. p. 193° (Found: C, 76·5; H, 5·1%).

Hydrolysis of Triethyl cis-3-*Methyl*cyclo*propane*-1 : 1 : 2-*tricarboxylate*.—Triethyl *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylate, b. p. 158—172°/18 mm., was prepared in up to 70% yield by Goss, Ingold, and Thorpe's method (*J.*, 1923, **123**, 3352) (although 96 g. of sodium was presumed to be a misprint for 9·6 g.). It has since been observed by Mr. R. J. D. Smith that continuous illumination with ultra-violet light reduces the time of reaction of bromine with ethyl crotonate from several days to 2—3 hr.

(i) [With Miss M. W. Lowe.] The triethyl ester (29 g.) was boiled during 30 hr. with 20% hydrochloric acid (200 ml.) under a short air-condenser that permitted loss of alcohol vapour, following Goss, Ingold, and Thorpe (*loc. cit.*). Additional hydrochloric acid was added to maintain the volume. Complete evaporation and keeping the residue in vacuum on a porous tile gave a crystalline solid (8·3 g.). Crystallised from a large volume of benzene this gave (what is considered to be) γ-methylparaconic acid as triangular plates, m. p. 78—79°. Fittig (*Annalen*, 1889, **255**, 18) gives m. p. 78—79°.

(ii) The triethyl ester (44·5 g.) was boiled with 1 : 1 aqueous hydrochloric acid (270 ml.) under a water-condenser (the ester appeared to be steam-volatile). As soon as homogeneity was attained (2·5 hr.) the solution was evaporated under reduced pressure. Prolonged keeping of the gummy acid in a vacuum gave a semi-solid mass, which resisted treatment with ether and benzene. Eventually ethyl acetate extracts were found to deposit a microcrystalline solid, *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid (5·0 g.), m. p. 208° with evolution of vapour. Preisweck (*Ber.*, 1903, **36**, 1085) recorded m. p. 215° (decomp.). No further crystalline product was obtained.

(iii) The triethyl ester (48 g.) and potassium hydroxide (40 g., 4 equiv.) in ethanol (400 ml.) were heated to reflux during 2·5 hr. Some deposition of the monoethyl dipotassium salt occurred as observed by Preisweck (*loc. cit.*). However, working up at this stage disclosed that hydrolysis was incomplete. Hence ester plus acid (42 g.), recovered by continuous ether-extraction, and potassium hydroxide (40 g.) in water (400 ml.) were refluxed for a further 2 hr. After continuous ether-extraction of the hydrolysate and rejection of the small oily extract, the aqueous solution was acidified with concentrated hydrochloric acid and again continuously ether-extracted. Evaporation and evacuation of the extract gave semisolid acid (30·5 g.). Trituration of the solid with cold ethyl acetate gave slightly impure *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid (15·0 g.). Crystallisation by percolation with boiling ethyl acetate raised the m. p. to a constant value of 207° (decomp.).

cis-3-*Methyl*cyclo*propane*-1 : cis-2-*dicarboxylic Acid*.—The above tricarboxylic acid (5·0 g.) was melted and kept at 225° until vapour evolution was complete (30 min.). The resultant gummy anhydride was warmed with water until it dissolved. The solution was treated with decolorising carbon and then evaporated under reduced pressure to a gum which was dissolved in boiling benzene, and the remaining water was removed by azeotropic distillation. Slow crystallisation of solvated acid took place as clusters of prisms which became opaque on drying (2·0 g.). Fractional crystallisation from benzene did not separate any less soluble *trans*-acid (cf. Goss, Ingold, and Thorpe, *loc. cit.*) but all the fractions had vague m. p.s in the range 90—120° with evolution of solvent. Storage at 100°/0·03 mm. during 1 hour gave liquids which after solidification still had m. p.s *ca.* 95—105° (Found: equiv., 71·5). Nevertheless, this product was substantially *cis-cis*-acid for the main fraction readily gave pure derivatives. The di-*p*-nitrobenzyl ester crystallised from ethanol in plates, m. p. and mixed m. p. 137° (corr.), and the di-*p*-phenylphenacyl ester crystallised from 1 : 1 acetone–ethanol as plates, m. p. and mixed m. p. 179° (corr.).

The *di*-p-*bromophenacyl ester* crystallised from ethanol in flattened needles, m. p. 166° (corr.) (depressed to 150° on admixture with the isomer of m. p. 171°) (Found: C, 49·2; H,

3·3; Br, 29·9. $C_{22}H_{16}O_6Br_2$ requires C, 49·1; H, 3·4; Br, 29·7%). From the concentrated filtrates from this ester a few crystals of different type separated and were picked out. Recrystallisation gave an isomeric *di*-p-*bromophenacyl ester*, m. p. 123·5° (corr.), as prisms from ethanol (Found: C, 49·1; H, 3·3; Br, 29·9%), presumably derived from 3-methyl*cyclo*propane-1 : *trans*-2-dicarboxylic acid.

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KING'S COLLEGE (UNIVERSITY OF LONDON), STRAND, W.C.2. [*Received, November 6th*, 1954.]

Reactions in Boron Trifluoride–n-Butyl Alcohol–Tri-n-butyl Borate Systems.

By M. F. LAPPERT.

[Reprint Order No. 5641.]

n-Butyl difluoroboronite, $BuO{\cdot}BF_2$, was obtained by action of boron trifluoride on tri-*n*-butyl borate, the reaction being reversible at high temperatures. Di-*n*-butyl fluoroboronate, $(BuO)_2BF$, could not be isolated by reaction of boron trifluoride and tri-*n*-butyl borate (2 mols.) or from the latter and the difluoroboronite. The difluoroboronite reacted with pyridine to give pyridine–boron trifluoride and tri-*n*-butyl borate, with solid sodium hydroxide to give *n*-butanol, with water to give a boron trifluoride–di-*n*-butanol complex, $BF_3,2BuOH$, and boric acid, and with *n*-butanol to give the same complex and a 1 : 1 : 1 compound between boron trifluoride, *n*-butanol, and tri-*n*-butyl borate. These compounds were identified by reaction with water, sodium hydroxide, pyridine, boron trifluoride, and tri-*n*-butyl borate, and by thermal degradation and each also by synthesis. Their structures are discussed.

THE original aim of this investigation was to prepare difluoroboronites ($RO{\cdot}BF_2$) and fluoroboronates [$(RO)_2BF$] and to compare and contrast methods of preparation and properties of these compounds with the corresponding chlorine analogues. Such fluorine compounds have received scant attention. Gasselin (*Ann. Chim. Phys.*, **1894**, **3**, 5) reported the preparation of the methyl esters from sodium methoxide and boron trifluoride, and from boron trifluoride and trimethyl borate. These results are contrary to the findings of Meerwein and Pannwitz (*J. pr. Chem.*, **1934**, **141**, 123) who by the former reaction obtained a co-ordination compound $BF_3,NaOMe$. Goubeau and Lücke (*Annalen*, **1951**, **575**, 37) prepared the same methyl esters, by using Gasselin's second method, and deduced from Raman-spectra investigations that the difluoroboronite was dimeric. Similar conclusions had been drawn by Allen and Sugden (*J.*, **1932**, 760) from parachor measurements, but methods of preparation were not stated. Goubeau and Lücke (*loc. cit.*) observed that dimethyl fluoroboronate, although having a constant b. p. (52·7°), could not be crystallised on cooling, but instead afforded the difluoroboronite, presumably by disproportionation: $2(MeO)_2BF \longrightarrow (MeO)_3B + MeO{\cdot}BF_2$. Meerwein, Battenberg, Gold, Pfeil, and Willfang (*J. pr. Chem.*, **1939**, **154**, 83) suggested that boron trifluoride formed 1 : 1 and 2 : 1 co-ordination complexes with trialkyl borates and that these were very unstable, tending to disproportionate into difluoroboronites and fluoroboronates. Cook, Ilett, Saunders, and Stacey (*J.*, **1950**, 3125) attempted to prepare di-*n*-butyl fluoroboronate by interaction of the boron trifluoride–diethyl ether complex and tri-*n*-butyl borate, but a very unstable compound was obtained, which suggested disproportionation of similar type to that observed by Goubeau and Lücke.

Of the methods available for the preparation of analogous chlorine esters having primary alkyl groups, namely, the interaction of boron trichloride with alcohols, ethers, or trialkyl

borates in appropriate proportions (Wiberg and Sütterlin, *Z. anorg. Chem.*, 1931, **202**, 1, 22, 31; Gerrard and Lappert, *J.*, 1951, 2545; 1952, 1486) the first two could not be applied in the fluorine system, since both alcohols and ethers form co-ordination complexes of types BF_3,ROH, BF_3,2ROH, BF_3,R_2O (for references see Greenwood and Martin, *Quart. Reviews*, 1954, **8**, 1).

The present paper deals with the *n*-butyl series. Boron trifluoride reacted readily with tri-*n*-butyl borate, 2 mols. of the gas being absorbed and *n*-butyl difluoroboronite obtained in good yield: $(BuO)_3B + 2BF_3 \longrightarrow 3BuO{\cdot}BF_2$. When $\frac{1}{2}$ mol. of the gas was used, the reaction took the same course and not according to $2(BuO)_3B + BF_3 \longrightarrow 3(BuO)_2BF$; neither was the fluoroboronate obtained by reaction of the borate and the difluoroboronite: $(BuO)_3B + BuO{\cdot}BF_2 \longrightarrow 2(BuO)_2BF$, although both these reactions proceeded quantitatively and readily (*e.g.*, at −80°) in the corresponding chlorine systems (Gerrard and Lappert, *loc. cit.*). It is possible that the elusiveness of the fluoroboronate is due to its disproportionation, and therefore the borate and difluoroboronite were mixed at −80° and pyridine was added in an effort to "fix" the equilibrium as a pyridine complex. However, the reaction observed was that given by the difluoroboronite (see below). A final attempt to isolate the fluoroboronate was by reaction of the difluoroboronite with *n*-butanol, the chlorine system [$BuO{\cdot}BCl_2 + BuOH \longrightarrow (BuO)_2BCl + HCl$] being again taken as an analogy. The reaction actually proceeded as follows:

$$3BuOH + 3BuO{\cdot}BF_2 \longrightarrow BF_3,(BuO)_3B,BuOH + BF_3,2BuOH$$

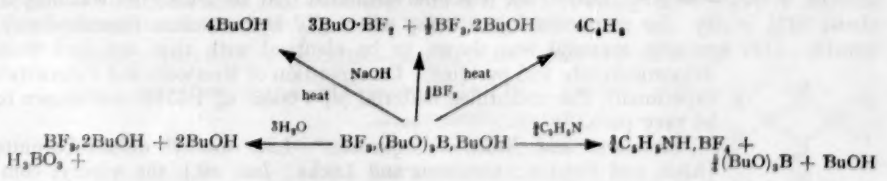
Addition of excess of *n*-butanol to the difluoroboronite gave the same products. Hydrolysis of the difluoroboronite also yielded boron trifluoride–di-*n*-butanol:

$$2BuO{\cdot}BF_2 + 3H_2O \longrightarrow BF_3,2BuOH + H_3BO_3 + HF \text{ (not isolated)}$$

whereas reaction with solid sodium hydroxide gave *n*-butanol quantitatively.

On heating the difluoroboronite at 120° for 30 hr., disproportionation (72%) was observed: $3BuO{\cdot}BF_2 \longrightarrow 2BF_3 + (BuO)_3B$. With pyridine, no co-ordination compound could be isolated, by contrast again with the dichloroboronite (Lappert, *J.*, 1953, 667), but pyridine–boron trifluoride and *n*-butyl borate were obtained: $3BuO{\cdot}BF_2 + 2C_5H_5N \longrightarrow BF_3,C_5H_5N + (BuO)_3B$.

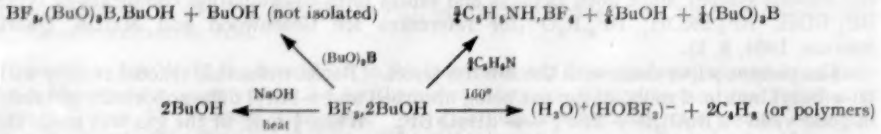
The 1 : 1 : 1 *Boron Trifluoride–*n*-Butanol–Tri-*n*-butyl Borate Complex.*—This represents a new type of 1 : 1 : 1 boron trifluoride co-ordination compound (see Greenwood and Martin, *loc. cit.*), whose composition was suggested by the following reactions:



It is a colourless liquid, which fumes slightly in moist air. On hydrolysis of this complex, boron trifluoride–di-*n*-butanol was obtained as shown above, but as this itself also underwent hydrolysis the yields were not quantitative. The 1 : 2 compound was also obtained by reaction with boron trifluoride, the difluoroboronite being the other product. Reaction with solid sodium hydroxide under reflux converted all butoxy-groups into *n*-butanol. Pyridinium tetrafluoroborate was obtained as a white precipitate by reaction with pyridine in *n*-pentane, tri-*n*-butyl borate and *n*-butanol being the other products. The 1 : 1 : 1 compound was quite unaffected by 3 hours' heating at 180°, but prolonged heating at this temperature afforded butene and a smaller quantity of higher olefins, probably polybutenes.

The composition of the 1 : 1 : 1 complex was further confirmed by the following synthesis: $BuOH + (BuO)_3B + BF_3 \longrightarrow BF_3,(BuO)_3B,BuOH$, a quantitative yield being obtained.

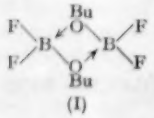
Boron Trifluoride–Di-n-butanol.—The formulation is in agreement with the following reaction scheme:



When the complex was heated with solid sodium hydroxide both the butoxy-groups were converted into *n*-butanol, but heating it alone at 160° for 15 min. resulted in complete decomposition to olefin (32% butene; 47% polybutenes) and hydroxonium trifluorohydroxyborate (Greenwood and Martin, *loc. cit.*). This was probably contaminated with 5—10% of difluorodihydroxyboric acid, $H^+[(OH)_2BF_2]^-$, which is obtained slowly by heating the hydroxonium fluorohydroxyborate (McGrath, Stack, and McCusker, *J. Amer. Chem. Soc.*, **1944**, **66**, 1263). The polymerisation of olefins in the presence of boron trifluoride or its complexes has been reported in B.P., 1936, 453,854, and the decomposition of boron trifluoride–di-*sec.*-alcohol complexes to give the corresponding olefin and hydroxonium fluorohydroxyborate has been mentioned by Meerwein and Pannwitz (*loc. cit.*). The physical constants obtained by these workers for the hydroxonium fluorohydroxyborate and its dioxan complex were used to identify the same compound in this investigation, and in addition a pyridine derivative was prepared by addition of pyridine. This is probably a 1 : 1 : 1 compound of composition BF_3,H_2O,C_5H_5N: $C_5H_5N + BF_3,2H_2O \longrightarrow BF_3,H_2O,C_5H_5N + H_2O$.

Even on milder heating, boron trifluoride–di-*n*-butanol decomposed; *e.g.*, a specimen of b. p. 85°/7 mm. (oil-bath at 110°), n_D^{20} 1·3725, d_4^{20} 1·049, was contaminated with about 9% of the fluorohydroxyborate (b. p. 72—74°/7 mm.). When distilled at 46·5°/0·1 mm. (oil-bath at 70°), it was 98·2% pure (n_D^{20} 1·3776, d_4^{20} 1·026). The estimates of purity were confirmed by the reaction with pyridine, by which almost theoretical quantities of *n*-butanol and tri-*n*-butyl borate were obtained, but the pyridine precipitate was more than expected for pyridinium tetrafluoroborate and was in fact a mixture of the latter and the pyridine derivative of hydroxonium fluorohydroxyborate formed as shown above from fluorohydroxyboric acid.

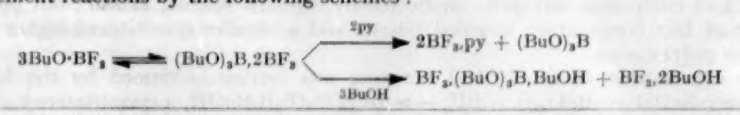
Boron trifluoride–di-*n*-butanol was synthesised by Meerwein and Pannwitz (*loc. cit.*) by passing boron trifluoride gas through *n*-butanol until the correct weight was absorbed: $2BuOH + BF_3 \longrightarrow BF_3,2BuOH$, but it is now estimated that their material was only of about 93% purity, the remainder again being essentially hydroxonium fluorohydroxyborate. This synthetic material was shown to be identical with that obtained from difluoroboronite and pyridine. On repetition of Meerwein and Pannwitz's experiment, the undistilled material (d_4^{20} 1·0053, n_D^{20} 1·3799) was shown to be very pure.



(I)

*Structures and Reaction Sequences.**—Like methyl difluoroboronite (Allen and Sugden; Goubeau and Lücke; *locc. cit.*), the *n*-butyl compound is also dimeric. Structure (I), similar to that proposed for the methyl ester, represents its probable constitution.

The reactions of *n*-butyl difluoroboronite may perhaps be better understood if a borate–boron trifluoride complex, $(BuO)_3B,2BF_3$, is postulated as an intermediate. Such compounds have been observed by Meerwein *et al.* (*loc. cit.*) and are very unstable, disproportionating to difluoroboronites: $(BuO)_3B,2BF_3 \rightleftharpoons 3BuO{\cdot}BF_2$. The reactions of the difluoroboronite with pyridine and *n*-butanol could then be represented as displacement reactions by the following schemes:



* The author is indebted to a referee for some of the suggestions contained in this section, and for suggesting the advisability of determining the conductivity of the ternary complex.

Meerwein (*Ber.*, **1933**, **66**, 411) has shown that addition of boron trifluoride–di-*n*-butanol to nitrobenzene markedly increases its conductivity. This is indicative of a salt-like structure, and since the 1 : 2 complexes with boron trifluoride with methanol and with *n*-propanol have been proved to be of type (II) (Greenwood and Martin, *J.*, 1953, 757, 1427), it appears probable that the *n*-butyl compound is analogous in structure, and not of type (III) or of the type (IV), proposed by Meerwein and Pannwitz (*loc. cit.*), which accounts for the structure in terms of hydrogen-bonding. Thus boron trifluoroide–di-*n*-butanol is probably *n*-butoxonium *n*-butoxytrifluoroborate, but as no direct evidence is available, non-committal nomenclature has been used in this paper.

$(ROH_2)^+(RO{\cdot}BF_3)^-$ (II) $\quad (R_2OH)^+(HO{\cdot}BF_3)^-$ (III) $\quad$ R, R: H–O · · · · · · H–O · · · BF_3 (IV)

Greenwood and Martin (*Quart. Reviews*, 1954, **8**, 1) have suggested that 1 : 1 : 1 complexes of boron trifluoride are ionic; *e.g.*, the complexes BF_3,ROR′,R″F (Meerwein *et al.*, *J. pr. Chem.*, **1937**, **147**, 251; **1939**, **154**, 83) were considered to have structure $[RR'R''O]^+BF_4^-$. The observation now made (p. 790) that the complex BF_3,$(BuO)_3B$,BuOH conducts electricity in the molten state would support a salt-like structure also for this complex. The specific conductivity of $\kappa_{20} = 9{\cdot}4 \pm 0{\cdot}4 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ is equivalent to a molar conductivity $\lambda_{M,20}$ of $3{\cdot}76 \pm 0{\cdot}16 \times 10^{-1}$ ohm^{-1} cm.^{2}. This molar conductivity is of the same order as that of boron trifluoride complexes whose structures have been proved to be ionic (*e.g.*, BF_3,2Pr^{n}OH is $[Pr^nOH_2]^+[Pr^nO{\cdot}BF_3]^-$ and $\lambda_{M,25} = 6{\cdot}8 \times 10^{-1}$ ohm^{-1} cm.^{2}; Greenwood and Martin, *loc. cit.*). Possible structures would be (V) or (VI). These indicate tri-*n*-butyl borate solvation of a proton (V) or a

$[(BuO)_3BH]^+[BuO{\cdot}BF_3]^-$ (V) $\quad [(BuO)_3B{\cdot}Bu^n]^+[HO{\cdot}BF_3]^-$ (VI)

n-butylcarbonium cation (VI), presumably by the attraction of these cations for the lone pairs of electrons on the oxygen atoms of the borate molecule. Although no evidence is available to distinguish between these possibilities, (V) appears the more probable. This view is taken because for all boron trifluoride complexes, whose structures have been evaluated, where there has been an apparent possibility of either a proton or a carbonium cation, the former has proved to be the true structure (*e.g.*, BF_3,MeOH is $H^+[BF_3{\cdot}OMe]^-$ and not $Me^+[HO{\cdot}BF_3]^-$). Moreover, if (II) is assumed as the structure of boron trifluoride–di-*n*-butanol, then the easy interconversions of this with the 1 : 1 : 1 complex are better appreciated in terms of (V), and the reactions may then be considered as cationic displacement reactions, according to the following schemes:

$$[BuOH_2]^+[BuO{\cdot}BF_3]^- + (BuO)_3B \longrightarrow [(BuO)_3BH]^+[BuO{\cdot}BF_3]^- + BuOH$$

$$[(BuO)_3BH]^+[BuO{\cdot}BF_3]^- + 3H_2O \longrightarrow H^+[BuO{\cdot}BF_3]^- \text{ (unstable)} + 3BuOH + H_3BO_3$$

$$\longrightarrow [BuOH]_3^+[BuO{\cdot}BF_3]^-$$

Experimental

Interaction of Boron Trifluoride and Tri-n-*butyl Borate.*—(*a*) Boron trifluoride (*Inorg. Synth.*, **1939**, **1**, 21) was passed through tri-*n*-butyl borate (12·30 g.) at 0° until no more gas was absorbed (1 hr.). The increase in weight was 7·40 g. (Calc. for BF_3, 2 mols.: 7·64 g.). On distillation n-*butyl difluoroboronite* (17·64 g., 90%), b. p. 56—59°/35 mm., was collected, which on redistillation had b. p. 43°/11 mm., n_D^{22} 1·3858, d_4^{20} 1·122 (Found: C, 39·6; H, 7·6; F, 30·7. $C_4H_9OBF_2$ requires C, 39·4; H, 7·5; F, 31·1%).

(*b*) In another experiment the trifluoride was passed through the ester (20·00 g.) until 2·60 g. of the gas had been absorbed (Calc. for BF_3, $\frac{1}{2}$ mol.: 2·96 g.). Distillation afforded *n*-butyl difluoroboronite (6·92 g., 99%), b. p. 55—57°/32 mm., n_D^{18} 1·3893, a middle fraction (1·61 g.), b. p. 60—113°/32 mm., n_D^{19} 1·4040, tri-*n*-butyl borate (13·81 g.), b. p. 113—115°/19 mm., n_D^{18} 1·4100 (Found: B, 4·70. Calc. for $C_{12}H_{27}O_3B$: B, 4·72%), and residue (0·27 g.). The yields in these experiments are based on $(BuO)_3B + 2BF_3 \longrightarrow 3BuOBF_2$.

The molecular weight of the difluoroboronite, determined cryoscopically in *cyclo*hexane, showed the compound to be dimeric (Found: *M*, 256, 248. Calc. for $C_8H_{18}O_2B_2F_4$: *M*, 244).

Action of Pyridine on n-*Butyl Difluoroboronite.*—To the difluoroboronite (4·60 g., 3 mols.)

in *n*-pentane (5 c.c.), pyridine (1·99 g., 2 mol.) was added at −80°, and the mixture was set aside for 24 hr. at 20°. The crystals (3·51 g., 95%) obtained, which were insoluble in *n*-pentane and ligroin but soluble in chloroform, were those of pyridine–boron trifluoride, m. p. 42—44° (Found: C_5H_5N, 53·7; F, 39·4. Calc. for C_5H_5N,BF_3: C_5H_5N, 53·7; F, 38·8%); the pentane filtrate afforded tri-*n*-butyl borate (2·53 g., 86%), b. p. 110—114°/20 mm., n_D^{19} 1·4112 (Found: B, 4·77%). The yield in this experiment is calculated on $3BuO{\cdot}BF_2 + 2C_5H_5N \longrightarrow 2C_5H_5N,BF_3 + (BuO)_3B$.

Action of Sodium Hydroxide on n-*Butyl Difluoroboronite.*—The difluoroboronite (8·70 g.) and sodium hydroxide (14·3 g.; a large excess) were heated at 130° for 3 hr., and then at 130°/0·5 mm. for 2 hr.; a mixture (5·90 g.) of *n*-butanol and water condensed in a trap cooled to −80°. When dried (Na_2SO_4) this afforded *n*-butanol (5·25 g., 99%), b. p. 114—117°/760 mm., n_D^{19} 1·4012.

Thermal Stability of n-*Butyl Difluoroboronite.*—The difluoroboronite (16·90 g.) was heated at 120° for 30 hr., a potassium hydroxide absorption tube being attached to the condenser. A loss of weight (4·55 g.) was observed, and boron trifluoride (4·53 g., 72%) [Found: B, 0·721 g. Calc. for BF_3 (4·53 g.): B, 0·721 g.] was trapped in the absorption tube. Distillation of the residue (12·27 g.) afforded unchanged *n*-butyl difluoroboronite (3·70 g., 22%), b. p. 55—60°/30 mm., n_D^{20} 1·3892, a middle fraction (1·40 g.), b. p. 65—75°/14 mm., n_D^{20} 1·3943, tri-*n*-butyl borate (7·12 g., 67%), b. p. 113—116°/14 mm., n_D^{19} 1·4108 (Found: B, 4·8%), and residue (0·09 g.). The yields in this experiment are based on $3BuO{\cdot}BF_2 \longrightarrow (BuO)_3B + 2BF_3$, and of this reaction 72% has taken place (based on the weight of BF_3) under the stated conditions.

Interaction of n-*Butyl Difluoroboronite and Tri-*n-*butyl Borate: An Attempt to establish the Existence of Di-*n-*butyl Fluoroboronate.*—The borate (7·91 g., 1 mol.) was added to the difluoroboronite (4·20 g., 1 mol.) at −80°, and the mixture kept at this temperature for 1 hr.; pyridine (10·9 g., 4 mols.) in *n*-pentane (30 c.c.) was then added. Two layers were formed: the upper, pentane layer on distillation afforded tri-*n*-butyl borate (10·48 g., 99%), b. p. 114—116°/18 mm.; n_D^{20} 1·4103 (Found: B, 4·7%). The lower layer slowly deposited crystals of pyridine–boron trifluoride (3·31 g., 98%), m. p. 44° (Found: C_5H_5N, 54·2%).

Action of n-*Butanol on* n-*Butyl Difluoroboronite.*—(*a*) The alcohol (27·3 g., 1 mol.) was added to *n*-butyl difluoroboronite (44·9 g., 1 mol.) at 20°. No hydrogen fluoride was evolved, but there was some heat of reaction. On distillation two main fractions were isolated: the 1 : 1 : 1 *compound* between boron trifluoride, *n*-butanol, and tri-*n*-butyl borate (44·3 g., 97%), b. p. 67—69°/12 mm., n_D^{20} 1·3980, d_4^{20} 0·929 (Found: C, 51·4, 52·6; H, 10·5, 10·3. $C_{16}H_{37}O_4B_2F_3$ requires C, 51·6; H, 10·1%); a middle fraction (2·86 g.), b. p. 74—88°/12 mm., n_D^{20} 1·3842; and *boron trifluoride–di-*n*-butanol* (21·8 g., 82%), b. p. 85—85·5°/7 mm., n_D^{20} 1·3725, d_4^{20} 1·049 (Found: C, 40·8, 41·2; H, 9·25, 9·60. $C_8H_{20}O_2,BF_3$ requires C, 44·4; H, 9·3%).

(*b*) The experiment was repeated, but distillation was carried out at 0·1 mm./<70° (bath temp.). The boron trifluoride–di-*n*-butanol, distilled three times, had b. p. 46·5—47°/0·1 mm., n_D^{20} 1·3776, d_4^{20} 1·026 (Found: C, 43·7; H, 9·60%).

(*c*) *n*-Butanol (3·81 g., 2 mols.) was added to *n*-butyl difluoroboronite (3·14 g., 1 mol.) at 20°, and hydrogen fluoride was not evolved. After 1 hr. at 20° the mixture gave on distillation *n*-butanol (1·94 g.), b. p. 39—45°/17 mm., the above 1 : 1 : 1 compound (3·26 g. Calc.: 3·20 g.), b. p. 67—70°/16 mm., n_D^{20} 1·3940, and boron trifluoride–di-*n*-butanol (1·51 g., 82%), b. p. 92—93°/16 mm., n_D^{20} 1·3760. The yields in these experiments are based on $3BuOH + 3BuO{\cdot}BF_2 \longrightarrow BF_3,(BuO)_3B,BuOH + BF_3,2BuOH$.

Hydrolysis of n-*Butyl Difluoroboronite.*—From a number of experiments, it was found that the action of a limited quantity of water on the difluoroboronite afforded boron trifluoride–di-*n*-butanol, and that the best yields were obtained in the following typical experiment: water (2·48 g., 3 mols.) was added to the difluoroboronite (11·18 g., 2 mols.) at −80° and the mixture was heated at 100—110° for 4 hr. No hydrogen fluoride was evolved. Boric acid (1·797 g.) (Found: B, 17·3. Calc. for H_3BO_3: B, 17·5%) was filtered off, diethyl ether being used to wash the precipitate. The solvent was removed from the filtrate. Distillation afforded a forerun (1·55 g.), b. p. 72—84°/13 mm., the crude 1 : 2 *n*-butanol compound (8·59 g., 82%), b. p. 84—90°/13 mm., and a residue (0·35 g.). During the early stages of the distillation, a gas (possibly hydrogen fluoride) was evolved, and boric acid deposited. Redistillation of the second fraction afforded a pure specimen of boron trifluoride–di-*n*-butanol (5·60 g.), b. p. 89—90°/13 mm., n_D^{18} 1·3727, d_4^{20} 1·048. The yield in this experiment is based on $2BuO{\cdot}BF_2 + 3H_2O \longrightarrow BF_3,2BuOH + H_3BO_3 + HF$.

Titration of an aqueous solution of the difluoroboronite against standard sodium hydroxide

solution could not be used as an estimation, but titration in the presence of mannitol with phenolphthalein as indicator gave constant values and the equivalent was 67·5.

Interaction of Pyridine and the 1 : 1 : 1 *Complex.*—Pyridine (1·39 g., 4 mols.) in *n*-pentane (10 c.c.) was added to the boron compound (8·70 g., 4 mols.) at −80°. A white precipitate was formed instantly, and the mixture was set aside for 1 hr. at 20°. The precipitate, pyridinium fluoroborate (2·69 g., 92%), m. p. 210—211° (Found: C_5H_5N, 47·2. Calc. for C_5H_5N,HBF_4: C_5H_5N, 47·3%), was filtered off. The solvent was removed from the filtrate by evaporation at 20 mm., and the residue on distillation afforded *n*-butanol (0·68 g. Calc.: 0·43 g.), b. p. 26—30°/8 mm., n_D^{19} 1·4192, a middle fraction (0·28 g.), b. p. 30—98°/8 mm., n_D^{20} 1·4112, and tri-*n*-butyl borate (6·56 g., 97%), b. p. 98—99°/8 mm., n_D^{20} 1·4090 (Found: B, 4·71%). The yields in this experiment are based on $4[BF_3,(BuO)_3B,BuOH] + 3C_5H_5N \longrightarrow 3C_5H_6NBF_4 + 5(BuO)_3B + BuOH$.

Action of Sodium Hydroxide on the 1 : 1 : 1 *Complex.*—A mixture of solid sodium hydroxide (15·1 g.; large excess) and the boron compound (7·61 g.) was heated at 130° under reflux for 3 hr., and then at 130°/0·3 mm. for a further 6 hr. A mixture (6·0 g.) of water and *n*-butanol was condensed in a trap at −80° and when dried (Na_2SO_4) this afforded *n*-butanol (5·40 g., 89%), b. p. 114—117°/760 mm., n_D^{20} 1·4006. The yield in this experiment is based on $BF_3,(BuO)_3B,BuOH \longrightarrow 4BuOH$.

Interaction of Boron Trifluoride and the 1 : 1 : 1 *Complex.*—Boron trifluoride gas was bubbled into the boron compound (10·00 g.) at 20° until saturated. The reaction was exothermic; and distillation afforded *n*-butyl difluoroboronite (9·45 g., 96%), b. p. 40—43°/10 mm., n_D^{18} 1·3845, d_4^{20} 1·122, a middle fraction (0·32 g.), b. p. 45—82°/10 mm., n_D^{18} 1·3873, and boron trifluoride–di-*n*-butanol (2·91 g., 100%), b. p. 83—85°/10 mm., n_D^{18} 1·3720, d_4^{20} 1·050. The yield here is based on $2[BF_3,(BuO)_3B,BuOH] + 3BF_3 \longrightarrow BF_3,2BuOH + 6BuO{\cdot}BF_2$.

Hydrolysis of the 1 : 1 : 1 *Complex.*—Water (2·13 g., 3 mols.) was added to the boron compound (14·67 g., 1 mol.) at 20°; a vigorous reaction ensued and a white precipitate of boric acid (1·475 g.) (Found: B, 17·3. Calc. for H_3BO_3: B, 17·5%) was formed at once. The filtrate afforded unchanged 1 : 1 : 1 complex (7·1 g.), b. p. 37—38°/0·1 mm., n_D^{20} 1·3988, d_4^{20} 0·926, and boron trifluoride–di-*n*-butanol (2·84 g., 64%), b. p. 48—49°/0·1 mm., n_D^{20} 1·3734, d_4^{20} 1·040. A condensate (5·00 g.), n_D^{20} 1·3910, was collected at −80°, and on distillation a forerun (1·4 g.), b. p. 92—93°/760 mm., probably the water–*n*-butanol azeotrope, and *n*-butanol (2·90 g.), b. p. 116—117°/760 mm., n_D^{20} 1·3998, were collected. The yield is based on $BF_3,(BuO)_3B,BuOH \xrightarrow{3H_2O} BF_3,2BuOH + H_3BO_3 + 2BuOH$.

Thermal Degradation of the 1 : 1 : 1 *Complex.*—The boron compound (11·27 g.) was heated, a cold trap at −80° being connected to the outlet of the condenser. During 3 hr. with the heating-bath at 180° no condensate had collected, but after 14 hr. *n*-butene (5·14 g., 75% based on total conversion of alkyl group into olefin) (Found: *M*, 59·7. Calc. for C_4H_8: *M*, 56·0) had collected in the trap. Its identity was confirmed qualitatively by its decolorising effect on bromine, and quantitatively by the conversion of 2·70 g. into the dibromide (9·95 g., 96%), b. p. 164—166°/760 mm., d_4^{20} 1·803, by addition of a chloroformic solution of bromine, washing with aqueous sodium hydrogen sulphite, and fractional distillation from the solvent. The only fraction isolated (1·00 g.) from the residue had b. p. 72—140°/10 mm., n_D^{20} 1·4353, decolorised bromine-water, and was probably a mixture of polymerised olefins.

Synthesis of the 1 : 1 : 1 *Complex.*—Boron trifluoride (4·61 g., 1 mol.) was passed into a mixture of tri-*n*-butyl borate (15·59 g., 1 mol.) and *n*-butanol (5·00 g., 1 mol.) at 20°. The reaction was exothermic, and the mixture was set aside for 2 hr. Distillation afforded the 1 : 1 : 1 complex (24·10 g., 96%), b. p. 73—74°/22 mm., n_D^{20} 1·3977, d_4^{20} 0·929, and a residue (0·24 g.). The yield in this experiment is calculated on $(BuO)_3B + BuOH + BF_3 \longrightarrow BF_3,(BuO)_3B,BuOH$.

Equivalent Weights of the 1 : 1 : 1 *Complex and of Boron Trifluoride–Di-n-butanol.*—Both of these compounds had a characteristic acidity in water. On titration with sodium hydroxide, with phenolphthalein as indicator and in the presence of mannitol, the equivalents were 121·0 for the 1 : 1 : 1 complex (Calc.: *M*, 367) and 71·0 for boron trifluoride–di-*n*-butanol (Calc.: *M*, 216).

Interaction of Pyridine and Boron Trifluoride–Di-n-butanol.—Pyridine (2·55 g., 3·72 mols.) in *n*-pentane (10 c.c.) was added to the boron compound (7·61 g., 4 mols.) at −80°. A white precipitate was formed instantly, and after the mixture had been stored at 20° for 1 hr., this was filtered off and washed with pentane. The precipitate (5·258 g. Calc.: 4·415 g. of $C_5H_6NBF_4$) (Found: C_5H_5N, 47·2%) was a mixture of pyridinium tetrafluoroborate and the pyridine derivative of hydroxonium fluorohydroxyborate (see p. 790). The pentane filtrate on

distillation afforded *n*-butanol (3·00 g., 92%), b. p. 116—117°/760 mm., n_D^{18} 1·4023, a middle fraction (0·20 g.), b. p. 32—97°/8 mm., n_D^{18} 1·4063, and tri-*n*-butyl borate (1·62 g., 71%), b. p. 98—98·5°/8 mm., n_D^{18} 1·4110 (Found: B, 4·65%). There was a residue (0·05 g.). The yields are based on $4(BF_3,2BuOH) + 3C_5H_5N \longrightarrow 3C_5H_6NBF_4 + 5BuOH + (BuO)_3B$.

Action of Sodium Hydroxide on Boron Trifluoride–Di-n-butanol.—A mixture of the boron compound (6·32 g.) and solid sodium hydroxide (4·28 g.) was heated at 130° for 24 hr. and then at 130°/0·5 mm. for a further 4 hr. A condensate (4·10 g.) of *n*-butanol (3·70 g., 86%), b. p. 115—117°/760 mm., and water was collected in a trap at −80°. The yield in this experiment is based on $BF_3,2BuOH \longrightarrow 2BuOH$.

Lack of Reaction between Boron Trifluoride and Boron Trifluoride–Di-n-butanol.—Boron trifluoride was bubbled through the boron compound (11·70 g.) for 2 hr. The mixture was evacuated (8 mm.) and distilled, the unchanged boron compound (11·54 g., 99%), b. p. 80—82°/8 mm., n_D^{19} 1·3720, d_4^{20} 1·064, being obtained.

Interaction of Tri-n-butyl Borate and Boron Trifluoride–Di-n-butanol.—The borate (5·97 g., 1 mol.) and boron trifluoride–di-*n*-butanol (5·60 g., 1 mol.) were mixed at 20° and no heat change was observed. The mixture was set aside for 1 hr. at 20° and was then distilled, yielding the 1 : 1 : 1 compound (9·35 g., 98%), b. p. 67°/12 mm., n_D^{20} 1·3972, a middle fraction (0·30 g.), b. p. 67—85°/12 mm., and boron trifluoride–di-*n*-butanol (1·00 g.), b. p. 89°/12 mm., n_D^{20} 1·3764. The yield of 1 : 1 : 1 complex is based on $(BuO)_3B + BF_3,2BuOH \longrightarrow BF_3,(BuO)_3B,BuOH + BuOH$.

Thermal Degradation of Boron Trifluoride–Di-n-butanol.—The boron compound (7·70 g.) was heated (bath at 160°) for 15 min. *n*-Butene (1·27 g., 32%) was collected at −80° and characterised as the dibromide, b. p. 163—165°/760 mm., d_4^{20} 1·800. The remainder separated into two layers. The upper layer (2·60 g.) yielded a mixture of what are believed to be polybutenes (1·87 g., 47%), b. p. 30—150°/0·5 mm., n_D^{20} 1·4565, d_4^{20} 0·824 (Found: I.V., 263), and a waxy olefinic residue (0·43 g., 11%), which declorised bromine. The lower layer (3·73 g.), a dark red oil, afforded hydroxonium fluorohydroxyborate (3·00 g., 81%), b. p. 72—74°/7 mm., n_D^{20} 1·3235, d_4^{20} 1·624, as a viscous liquid, and a dark residue remained. The last-named compound was further characterised as the dioxan derivative, m. p. 138—140° (after 3 crystallisations from ether). Meerwein and Pannwitz (*loc. cit.*) give m. p. 142°. Yields in this experiment are based on $BF_3,2BuOH \longrightarrow BF_3,2H_2O + 2C_4H_8$ (and polymers).

Pyridine Derivative of Hydroxonium Fluorohydroxyborate.—Pyridine (1·315 g., 1·19 mol.) in *n*-pentane (10 c.c.) was added dropwise to hydroxonium fluorohydroxyborate (1·3940 g., 1 mol.) at −80°. The sticky, white precipitate was washed with ether. It (2·1029 g., 95%) was believed to be *pyridinium trifluorohydroxyborate* (Found: C_5H_5N, 46·4. $C_5H_7ONBF_3$ requires C_5H_5N, 47·8%).

Synthesis of Boron Trifluoride–Di-n-butanol.—Boron trifluoride (6·61 g., 1 mol.) was passed into *n*-butanol (15·05 g., 2 mols.) at 20°. The undistilled boron trifluoride–di-*n*-butanol had n_D^{20} 1·3799, d_4^{20} 1·0053 (Found: C, 44·3; H, 9·3%). On distillation, the fraction of b. p. 86°/8 mm. (19·52 g.) was collected; n_D^{20} 1·3722, d_4^{20} 1·041.

Repetition of the Pyridine Experiment on Synthetic Boron Trifluoride–Di-n-butanol.—(*a*) Pyridine (3·20 g., 1·34 mol.) in *n*-pentane (20 c.c.) was added dropwise to the undistilled boron compound (8·661 g., 1 mol.), prepared as above, at −80°. The mixture was set aside for 1 hr. at 20°, and pyridinium tetrafluoroborate (5·0259 g., 100%), m. p. 212° (Found: C_5H_5N, 47·2%), was filtered off and thoroughly washed with more pentane. (*b*) The experiment was repeated upon the distilled synthetic material (4·6337 g.) and pyridine (2·00 g.). The precipitate (3·0470 g. Calc.: 2·684 g.) had m. p. 200—208° (Found: C_5H_5N, 46·5%).

Electrical Conductivity of the 1 : 1 : 1 Complex.—The cell was dried in the oven for 1 hr. at 110° and filled with the highly purified sample (after a preliminary rinse) in a dry cabinet under a nitrogen atmosphere. The electrodes (platinum) were left in the cell for ¼ hr. after the first reading to make certain there was no change due to progressive hydrolysis. The conductivity of the molten $(BuO)_3B,BuOH,BF_3$ was $9·4 \pm 0·4 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ at 20°.

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The Exchange of Oxygen between Alcohols and Water. Part I. Rates of Carbonium-ion Formation and Decomposition in Acidic Aqueous Solutions of tert.*-Butanol.*

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The rates of oxygen exchange between *tert.*-butanol and water and the rates of the dehydration in the presence of sulphuric acid have been determined at a number of temperatures and acid concentrations. The rate coefficient for the formation of carbonium ion from the alcohol at 55° is $1{\cdot}33 \times 10^{-4}$ sec.$^{-1}$ (for unit activity H^+) and the activation energy associated with the process is 30·1 kcal./mole. The activation energy for the formation of *iso*butene from the *tert.*-butyl carbonium ion is 2·2 kcal./mole. The analysis permits the identification of the rate of hydration of *iso*butene with the rate of formation of the carbonium ion from the olefin. In the dehydration the rate-controlling step is the formation of the carbonium ion *via* the hydroxonium ion, whereas the rate-controlling step of the hydration is the protonation of the olefin. The rates of these reactions are compared with calculated values and with the rates of other similar reactions.

Many reactions of alcohols in aqueous acidic media, and particularly those of tertiary alcohols, are assumed to proceed through the intermediate formation of a carbonium ion. In reactions such as ether formation, acid-catalysed esterification, and dehydration of these alcohols the initial steps are commonly represented as

$$ROH + H_3O^+ \rightleftharpoons ROH_2^+ + H_2O \qquad ROH_2^+ \rightleftharpoons R^+ + H_2O \quad . \quad . \quad . \quad (1)$$

It is further assumed that the dissociation of the oxonium compound is rate-determining for these reactions.

The purpose of the present series of papers is to determine to what extent the assumption of a carbonium-ion intermediate is justified, and whenever possible to determine its rate of formation and decomposition. We now describe measurements of the rate of oxygen exchange between *tert.*-butanol (a typical tertiary alcohol) and water in the presence of various concentrations of sulphuric acid. Alcohol of normal isotopic composition was dissolved in acidified water enriched with respect to $H_2{}^{18}O$. Samples of alcohol were analysed for ^{18}O content after various intervals of time. The rate constants of the exchange reaction thus obtained are presented in Table 1, together with the rate constants of the dehydration of the alcohol observed under similar experimental conditions.

Table 1. *Rates of oxygen exchange between* tert.*-butanol* (1M) *and water in aqueous sulphuric acid solution, and the rates of the dehydration reaction* (10^5k, *sec.*$^{-1}$).

Acid concn., N	Exchange, 55°	Exchange, 75°	Dehydration, 55°	Dehydration, 75°
0·09	1·33	19·7	0·045	0·95
0·9	15·4	—	0·57	—

In acid aqueous media *tert.*-butanol undergoes a reversible dehydration and this process will lead to an observed oxygen exchange. The question whether the dehydration–hydration reaction proceeds through the carbonium ion or not may be answered by a comparison of the observed rates of their reaction with that of the exchange reaction. The reactions involved may be represented by the general scheme

$$\left.\begin{array}{rl} ROH + H_3O^+ & \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \; ROH_2^+ + H_2O \\ ROH_2^+ & \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \; R^+ + H_2O \\ R^+ + H_2O & \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \; P + H_3O^+ \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where P represents the olefin (*iso*butene in this case).

We shall not yet make any assumptions regarding the relative magnitudes of the rate coefficients k_3, k_4, k_5, and k_6, and shall derive them from the experimental data. We can derive for the rate of olefin elimination (and of alcohol dehydration) the equation

$$d[P]/dt = -d[ROH]/dt = k'[ROH] - k''[P]$$

where $$k' = k_3k_5K[H_3O^+]/(k_4 + k_5)[H_2O]; \quad K = k_1/k_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

and $$k'' = k_4k_6[H_3O^+]/(k_4 + k_5). \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3b)$$

For the isotopic exchange reaction we can similarly obtain the equation

$$dN/dt = (N_\infty - N)\{([ROH] + [H_2O])/[H_2O]\}\{k_4[H_3O^+]/(k_4+k_5)\}\{k_3K/[H_2O] + k_6[P]/[ROH]\} \quad (4)$$

where N is the mole-fraction of $R^{18}OH$ in the alcohol at any time and N_∞ is the value at isotopic equilibrium. In this equation [P] and [ROH] are time-variable, and the integration leads to equations which are not particularly useful. If, however, we start with a system containing water, olefin, and alcohol at their equilibrium total concentrations but with the water and alcohol differing in their isotopic compositions, equation (4) can be integrated readily since now [P] and [ROH] are constant and their ratio is determined by the equilibrium constant of the dehydration–hydration reaction:

$$[P_\infty]/[ROH_\infty] = k_3k_5K/k_4k_6[H_2O] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The rate coefficient for the exchange reaction then becomes

$$k_{exch} = \{([ROH]_\infty + [H_2O])/[H_2O]\}k_3K[H_3O^+]/[H_2O] \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Comparing equations (3) and (5), we note that

$$k' = k_{exch.}\{[H_2O]/[([H_2O] + [ROH]_\infty)]\}k_5/(k_4 + k_5) \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Since $[H_2O]/([H_2O] + [ROH])$ is very nearly unity, it follows that k' will be always smaller than $k_{exch.}$. A comparison of the experimentally determined coefficients $k_{exch.}$ and k' permits therefore the computation of the ratio k_4/k_5. Once this ratio is available it can be substituted in equation (3*b*) to obtain a value for $k_6[H_3O^+]$. Under our experimental conditions the equilibrium of the dehydration–hydration reaction is reached much sooner than that of the isotopic exchange. Therefore it is sufficient to delay the measurement of the exchange reaction by several half-lives of the olefin reaction to ensure that it is proceeding under conditions of chemical equilibrium.

In the equations derived above, concentrations are used rather than activities. The errors introduced by this simplification cannot affect the arguments presented below and therefore no attempt was made to determine, by separate experiments, the appropriate activity coefficients.

Values for k' and k'' for the dehydration and hydration reactions have been reported by Lucas and Eberz (*J. Amer. Chem. Soc.*, 1934, **56**, 460), Eberz and Lucas (*ibid.*, p. 1234), and by Levy, Taft, Aaron, and Hammett (*ibid.*, 1951, **73**, 3792). All these values have been obtained in essentially aqueous media and with nitric acid as catalyst. Since in our case the exchange reactions were carried out in a medium which contained an appreciable amount of alcohol (about 10 vols. %), considerable corrections are necessary in comparing the data. These corrections have to allow for the effect of solvent on the rate of the reaction and on the activity of the catalyst. To avoid such corrections, which are at best approximations, we have carried out independent measurements of the dehydration reaction under conditions as close as possible to those used in the exchange reactions. These are the values presented in Table 1. Our value for k' at 55° and 0·09N-acid, $0{\cdot}45 \times 10^{-6}$ sec.$^{-1}$, may be compared with that of Levy, Taft, Aaron, and Hammett (*loc. cit.*), $1{\cdot}67 \times 10^{-6}$ sec.$^{-1}$, and that calculated from Eberz and Lucas's lower-temperature experiments (*loc. cit.*), *viz.*, $1{\cdot}63 \times 10^{-6}$ sec.$^{-1}$. The approximately four-fold rate coefficient in the highly aqueous solvent as compared with the more alcoholic medium (1M-*tert.*-butanol) is in reasonable agreement with the expected solvent effects on these reactions (cf. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell, 1953, p. 453) and with our experiments in 0·1M-butanolic solutions ($1{\cdot}1 \times 10^{-6}$ sec.$^{-1}$ as calculated from data of Table 5.

Using the results of Table 1 and equation (6), we calculate for the ratio k_4/k_5 the value 29 in 0·1N-acid and 26 in 1N-acid at 55°, and 20 in 0·1N-acid at 75°. The decrease in the ratio k_4/k_5 with increasing temperature would indicate a slightly higher activation energy for process 5 as compared with process 4 [see equations (2)]. If one assumes that process 4, involving the recombination of a carbonium ion with a water molecule, possesses no activation energy, then it is possible to calculate an activation energy of about 2·2 kcal./mole for the decomposition of the carbonium ion to olefin. The ratio k_4/k_5 determines the proportion of olefin formed in other reactions involving carbonium ions, such as unimolecular solvolysis of *tert.*-butyl halides and sulphonium salts. It is therefore of some interest to compare the proportion of olefin elimination reported for such reactions with the values of k_4/k_5. No values are available for olefin elimination in highly aqueous solvents as used in our work, but making extreme extrapolation from media of lower water content (cf. Ingold, *op. cit.*, p. 459) and correcting our results to 25° by using the temperature coefficient as determined above, we estimate the proportion of olefin formed in the solvolysis of *tert.*-butyl bromide in "90%" ethanol as 3%, compared with 2·8% as calculated from the value of k_4/k_5 at 25°.

The fact that the rate constant for the exchange reaction is considerably greater than that of the dehydration reaction is sufficient to exclude the mechanism of exchange involving direct olefin elimination from the oxonium ion, *viz.*, $ROH_2^+ \rightleftharpoons P + H_3O^+$. Had this been the correct mechanism the rate coefficient of the exchange and dehydration reactions would be identical. Recently Levy, Taft, and Hammett (*J. Amer. Chem. Soc.*, 1953, **75**, 1253, 3955) showed that there is little or no *as*-ethylmethylethylene (2-methylbut-1-ene) formed when trimethylethylene is hydrated to *tert.*-amyl alcohol. From this observation they concluded that . . . "The reaction scheme consisting in the rapid and reversible addition of a proton to the olefin, followed by a rate-determining reaction of the ion with a water molecule, is definitely excluded as the mechanisms of the hydration reaction." In other words, in equation (2), k_4 cannot be smaller than k_5 or k_6, in complete agreement with our findings. Levy, Taft, and Hammett (*loc. cit.*), however, were led to assume the direct elimination of olefin from the oxonium ion. From the arguments presented above it will be seen that this conclusion is not warranted and that all that is necessary to explain the failure to observe the interconversion of the olefins is that k_4 be sufficiently greater than k_5 (for each olefin).

Although the evidence presented in this paper does not rigorously exclude the possibility of exchange by a bimolecular attack of a water molecule on the oxonium ion, $H_2{}^{18}O + ROH_2^+ \rightleftharpoons R^{18}OH_2^+ + H_2O$, we consider that for a tertiary alcohol in a highly aqueous medium this is an unlikely mechanism. The operation of this mechanism in other alcohols is discussed in a subsequent paper.

Accepting the mechanism depicted in equation (2), we may identify the observed rate coefficient for the exchange reaction, as determined under gross chemical equilibrium conditions, as approximately equal to

$$k_{exch.} \approx k_3 K[H_3O^+]/[H_2O] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Similarly, using equation (3*b*), we may identify k'', the rate constant of the hydration reaction, with $k_6[H_3O^+]$.

The observed activation energies for the exchange and hydration reaction can also be identified with the corresponding steps. The value of 30·5 kcal./mole, calculated from the rates of exchange at 55° and 75°, corresponds to the heat of activation of the ionisation step 3 plus the difference in the heat of activation of steps 1 and 2. Our value should be compared with 34·8 kcal./mole, as determined by Eberz and Lucas (*loc. cit.*), and 34·1 kcal./mole, as calculated by Franklin (*Trans. Faraday Soc.*, 1952, **48**, 443). The hydration reaction (6) possesses the lower activation energy of 23·4 kcal./mole (Lucas and Eberz, *loc. cit.*). The relatively high activation energy of the ionisation step can be compared with the activation energy of the unimolecular decomposition of sulphonium ions. Thus *tert.*-butyldimethylsulphonium ion decomposes in water with an activation energy of 33 kcal./mole, a value close to that observed above for the decomposition of the oxonium ion.

The values of the various rate coefficients and activation energies determined in the present work are collected in Table 2, where they are compared with those from Franklin's calculation (*loc. cit.*).

TABLE 2. *Rate coefficients of the various steps in the acid-catalysed dehydration of* tert.*-butanol in aqueous media.*

Reaction	k (obs.)	E_A (obs.), kcal./mole	k (calc.) *	E_A (calc.),* kcal./mole
3	$1{\cdot}33 \times 10^{-4}$ †	30·1	$3{\cdot}1 \times 10^{-4}$ †	34·1
4	$(3{\cdot}8 \times 10^{14})$	0	$3{\cdot}8 \times 10^{14}$	0
5	$1{\cdot}3 \times 10^{13}$	2·2	$3{\cdot}8 \times 10^{14}$	0
6	—	—	$1{\cdot}45 \times 10^{-1}$	21·3

* Values calculated by Franklin corrected to 55° and expressed as bimolecular rate constants; k_4 and k_5 include the concentration of water (55·5 moles/l.).

† These rate coefficients are multiplied by the unknown equilibrium constant K. They represent therefore the rate of formation of carbonium ion from the alcohol according to the equation

$$ROH + H_3O^+ \rightleftharpoons R^+ + 2H_2O.$$

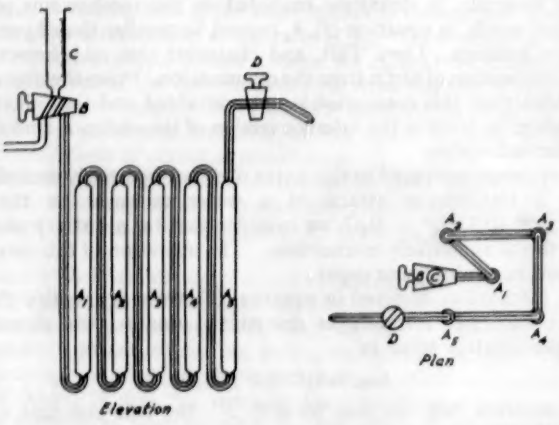
From the constants collected in Table 2 it is seen that the rate-determining step, in the sense of the slowest step in a series of reactions, for the dehydration reaction is the ionisation of the oxonium ion, and for the hydration reaction it is the protonation of the olefin (k_6).

EXPERIMENTAL

Materials.—Water containing about 2·8% of $H_2^{18}O$ was used throughout. It was purified by distillation from alkaline potassium permanganate.

tert.*-Butanol.* The commercial product was purified by refluxing it over sodium and fractionation through a 20-plate column. The distillate (m. p. 24·5°) was free from olefin.

All other reagents were of analytical grade.



Isotopic Exchange Reactions.—The apparatus used was similar to that of Lucas and Eberz (*loc. cit.*) and is shown in the Fig. The reaction system consisted of five vertical glass tubes ($A_1 \ldots A_5$), 18 cm. long and 15 mm. in inside diameter, connected in series by glass capillaries of 1·5 mm. inside diameter. One end of the apparatus is closed by a two-way capillary stopcock B, carrying a graduated separation funnel C (100 ml. capacity). The other end of the apparatus is closed with a capillary stopcock D with a drawn-out tip. The volume of the apparatus between stopcocks B and D was about 120 ml.

Stock solutions of sulphuric acid (1N and 0·1N) were prepared by adding a weighed quantity of the concentrated acid to ^{18}O-enriched water. Reaction mixtures for the exchange runs were prepared by adding a known weight of *tert.*-butanol to a weighed amount of the sulphuric acid stock solutions. The densities of the mixtures were measured in separate experiments, and their values used in calculating the molarities of the alcohol and acid.

The apparatus was filled by introducing the mixture through funnel C and stopcock B until

all the air had been displaced and surplus solution appeared at the tip of stopcock *D*, which was then closed. Mercury (50 ml.) was then poured into funnel *C* and a small amount was allowed to fill the capillary below *B* by manipulation of stopcock *D*. The whole apparatus was then submerged in a thermostat regulated to 0·01°. After an interval of at least six times the half-life for olefin formation, sampling was started. Samples (7 ml.) were withdrawn through stopcock *D* at intervals of time suitable for the application of Guggenheim's method of kinetic analysis (cf. *Phil. Mag.*, **1926**, **2**, 538). The samples were run into test tubes containing enough 10N-potassium hydroxide to neutralise the solution; anhydrous potassium carbonate (2 g.) was then added, and the mixture shaken vigorously, and then allowed to settle for 15 min. The bottom (aqueous) layer was removed with a fine pipette, and the alcohol layer dried with more anhydrous potassium carbonate. After 2 hr. over the desiccant, the alcohol was vacuum distilled. An equal volume of anhydrous potassium carbonate was again added, and the mixture shaken vigorously for 2 hr. at 50° and left overnight. The alcohol was finally separated by centrifuging and analysed for its ^{18}O content by Anbar, Dostrovsky, Klein, and Samuel's method (*J.*, 1955, 155). As an illustration of our method one run is represented in full in Table 3. where N_t represents the atom % of ^{18}O in alcohol at time t.

From the slope of a plot of log $(N_{t+300} - N_t)$ against t, the value of $19·7 \times 10^{-5}$ sec.$^{-1}$ was obtained for $k_{exch.}$

TABLE 3. ^{18}O *Exchange between* tert.*-butanol* (1·04M) *and water in aqueous sulphuric acid* (0·0913N) at 75·0°. *Initial* ^{18}O *content of aqueous reaction medium* 2·5 *atom* % $H_2{}^{18}O$.

Time (min.)	20	30	50	60	80	100	120
N_t	0·370	0·408	0·684	0·757	0·920	1·030	1·113
N_{t+300}	1·389	1·393	1·403	1·409	1·419	1·427	1·435
log $(N_{t+300} - N_t)$ ...	0·0082	$\bar{1}$·9663	$\bar{1}$·8570	$\bar{1}$·8141	$\bar{1}$·6981	$\bar{1}$·5985	$\bar{1}$·5076

Dehydration Experiments.—The apparatus used in this experiment was similar to that described by Levy, Taft, Aaron, and Hammett (*J. Amer. Chem. Soc.*, **1951**, **73**, 3792) except that the manometer had a total length of 100 cm. The total volume of the apparatus was 110·5 ml. The experimental procedure differed somewhat from that described by the above authors in that the starting material in our experiments was a dilute solution of the alcohol and not the olefin, and therefore the rate of pressure increase with time was observed. The reaction mixture was prepared by the method described for the exchange reactions. After being placed in the reaction vessel the solution was degassed by repeated freezing, evacuating, melting, and refreezing. The reaction vessel was then sealed under vacuum, and the apparatus placed in a thermostat. Pressure readings were taken at predetermined intervals. Experiments were repeated for various ratios of vapour space to liquid volume. For such conditions, and following the procedure of Levy, Taft, Aaron, and Hammett (*loc. cit.*), the following equation can be derived:

$$C_a^{\circ}/k_{obs.}p_{\infty} = r/RTh' + h/h' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where C_a° and p_{∞} are the initial alcohol concentration and final olefin partial pressure, respectively; r is the ratio of vapour space to solution volume; h = concentration of olefin/partial pressure of olefin; h' is the rate coefficient for the dehydration reaction (cf. p. 792) and $k_{obs.}$ is the observed rate coefficient as determined from the rate of pressure rise in the experiments described above. Plotting $C_a^{\circ}/k_{obs.}p_{\infty}$ against r, we obtain the values of h' presented in Table 1. As an illustration of our method one run is presented in full in Table 4.

TABLE 4. *Dehydration of* tert.*-butanol* (1·04M) *in aqueous sulphuric acid* (0·0858N) *at* 55°.

Time (min.)	7	17	27	52	67	87	122	147	192	207
P_t	198·0	208·3	217·8	239·0	250·2	264·1	284·7	296·9	314·9	320·8
P_{t+1320}	377·5	377·9	378·1	379·7	380·3	381·1	381·8	382·9	383·8	384·2
log $(P_{t+1320} - P_t)$ ...	2·2541	2·2294	2·2049	2·1483	2·1143	2·0682	1·9872	1·9345	1·8382	1·8021

Vol. of liquid phase 74·5 ml.; $r = 0·483$; $P_0 = 192·9$ mm. (from the linear extrapolation to zero time); P_{∞} (observed at 11 half-lives) = 384·2 mm.; $p_{\infty} = 191·3$ mm. Loss of alcohol from liquid phase = 0·38%.

From the plot of log $(P_{t+1320} - P_t)$ against time the value of $h = 8·7 \times 10^{-6}$ sec.$^{-1}$ was obtained.

Two further runs on the same mixture at the same temperature but with $r = 1·225$ and 1·862

gave values of k of $3{\cdot}7 \times 10^{-5}$ and $2{\cdot}4 \times 10^{-5}$ sec.$^{-1}$ and had p_∞ of 194·5 and 191 mm., respectively. From the slope of this straight line obtained on plotting $C_a^\circ/k_{obs.}p_\infty$ against r, the value of $4{\cdot}17 \times 10^{-7}$ sec.$^{-1}$ was obtained for k'.

Our experiments on the dehydration of *tert.*-butanol in media containing different amounts of the alcohol are summarised in Table 5.

TABLE 5. *Rate coefficients* ($\times 10^5$, *sec.*$^{-1}$) *of dehydration of* tert.*-butanol in aqueous sulphuric acid.*

Normality of acid, N	0·858	0·858	0·0858
Molarity of alcohol	0·104	1·04	1·04
Temperature 55·0°	1·03 *	0·528	0·0417
,, 75·0°	—	—	0·870

Temp. coeff. = 4·57 per 10°. Energy of activation = 34·5 kcal.

* Corrected value from observations in 0·952N-acid.

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Dithiobiurets. Part I. Some 1- *and* 1 : 5-*Substituted Derivatives.*

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Numerous 1- and 1 : 5-substituted dithiobiurets have been prepared for test as trypanocidal agents. A new method for the preparation of 1-monosubstituted dithiobiurets from alkyl dithiocarbamates has been developed.

THE observation of low but well-defined activity against *Trypanosoma congolense* in mice among a number of simple 1-aryldithiobiurets (Woolfe, *Brit. J. Pharmacol.*, 1953, **8**, 420) prompted us to extend our examination of this type of compound. This and the following paper describe the preparation for this purpose of a wide variety of dithiobiurets.

1-Substituted dithiobiurets were prepared for the most part by standard procedures. The first of these was by fusion of arylamines with 3-imino-5-thio-1 : 2 : 4-dithiazolidine (" perthiocyanic acid "), a method due to Glutz (*Annalen*, 1870, **154**, 44) and later developed by Tursini (*Ber.*, 1884, **17**, 584) and Fromm (*Annalen*, 1893, **275**, 20, and other papers). Crude products prepared by this method are frequently contaminated by sulphur which is difficult to eliminate by direct crystallisation. Precipitation from dilute sodium hydroxide solution with hydrogen sulphide was found to effect rapid purification, often with improved yields. Weakly basic amines either fail to react or, in certain cases, afford the amine thiocyanate as sole product.

The second method was that due to Wunderlich (*Ber.*, 1886, **19**, 452) and Hecht (*Ber.*, 1892, **25**, 749) whereby *iso*thiocyanates are condensed with sodium cyanamide to give *N*-cyanothioureas to which hydrogen sulphide is then added.

A third method was developed which may be regarded as a modification of the second. It was particularly useful since it avoids the preparation of the *iso*thiocyanate. It is known that dithiocarbamates of the type, $RNH{\cdot}CS_2R'$, decompose to RNCS and R'SH on gentle heating (von Braun, *Ber.*, 1902, **35**, 3368; Delépine, *Bull. Soc. chim.*, 1902, **27**, 809). It was therefore thought possible that alkyl dithiocarbamates might condense directly with sodium cyanamide to yield *N*-cyanothioureas. Such condensation does, in fact, occur in refluxing methanol or ethanol—whether directly or through the intermediate formation of the *iso*thiocyanate is not known—and further processing according to Hecht's method affords satisfactory yields of dithiobiurets.

By these methods dithiobiurets were prepared variously substituted in the 1-position with alkyl, aryl, substituted aryl, and heterocyclic radicals. Three bisdithiobiurets were also prepared.

1 : 5-Disubstituted dithiobiurets were prepared by condensation of the appropriate

*iso*thiocyanates and *S*-ethyl*iso*thioureas (cf. Curd, Davey, Richardson, and Ashworth, *J.*, 1949, 1739) and thiohydrolysis of the resulting 2-ethyl-2-*iso*dithiobiurets.

Since trypanocidal activity is frequently dependent on the presence of a quaternary ammonium grouping in the molecule, it was thought of interest to prepare a number of dithiobiurets possessing this feature. These were prepared by two methods. In the first, an *iso*thiocyanato-substituted base was quaternised and then converted by the cyanamide route into the corresponding dithiobiuret. Alternatively, the dithiobiuret residue of the unquaternised compound was first protected by conversion into its 2 : 4-dimethyl-2 : 4-di*iso*-derivative. The basic centre could then be quaternised and the protecting groups removed by thiohydrolysis. Neither these compounds nor the others described in this paper showed any significantly higher level of trypanocidal activity than that originally observed in 1-phenyldithiobiuret (Woolfe, *loc. cit.*).

Experimental

M. p.s vary with rate of heating and were therefore taken under standard conditions by placing the tube in the bath at 10° below the m. p. and raising the temperature by 2° per minute.

1-*Substituted dithiobiurets.*

(a) *From Amines and Perthiocyanic Acid.*—A mixture of the amine (0·2 mol.) and perthiocyanic acid (0·1 mol.) was heated in a steam-bath until either the yellow colour disappeared and a white solid product was obtained, or until the perthiocyanic acid had dissolved to give a clear solution (5 min. to 5 hr.). The mixture was then warmed with ethanol (30 c.c.), the suspension cooled, and N-hydrochloric acid (120 c.c.) added. The resulting precipitate was filtered off, washed with water, and triturated with 5N-sodium hydroxide. The suspension was diluted to 750 c.c. and filtered through kieselguhr, and the product precipitated with hydrogen sulphide and crystallised.

In this manner the following new dithiobiurets were prepared (time of heating and yield in parentheses): 1-m-*methoxyphenyl*- (35 min., 50%), felted needles (from ethanol), m. p. 173—174° (Found: N, 17·1. $C_9H_{11}ON_3S_2$ requires N, 17·0%); 1-p-*butoxyphenyl*- (30 min., 43%), plates (from ethanol), m. p. 161—162° (Found: N, 14·7. $C_{12}H_{17}ON_3S_2$ requires N, 14·8%); 1-*phenyl*-1-*propyl*- (5 hr., 37·5%), needles (from ethanol), m. p. 141—142° (Found: N, 16·4. $C_{11}H_{15}N_3S_2$ requires N, 16·6%); and 1-*butyl*-1-*phenyl*- (5 hr., 41%), plates (from ethanol), m. p. 136—137° (Found: N, 15·8. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

The following known dithiobiurets were prepared by the same method: 1-phenyl- (4 min., 43%), m. p. 183—184° (Fromm, *loc. cit.*, records m. p. 184°); 1-*o*-methoxyphenyl- (40 min., 37%), needles (from benzene) or plates (from aqueous methanol), m. p. 143—144° (Found: C, 44·8; H, 4·4; N, 17·0. Calc. for $C_9H_{11}ON_3S_2$: C, 44·8; H, 4·6; N, 17·4%) (Fromm, Brück, Runkel, and Mayer, *Annalen*, 1924, **437**, 106, record m. p. 148°); 1-*p*-methoxyphenyl- (25 min., 42%; prepared by Dr. P. E. Macey), plates (from ethanol), m. p. 173—174° (Swaminathan and Guha, *J. Indian Chem. Soc.*, 1946, **42**, 3350, record m. p. 165°); 1-*p*-ethoxyphenyl- (30 min., 40%), plates (from ethanol), m. p. 171—172° (Found: N, 16·6. Calc. for $C_{10}H_{13}ON_3S_2$: N, 16·5%) (Fromm and Vetter, *Annalen*, 1907, **356**, 178, record m. p. 178°); 1-*p*-tolyl- (10 min., 55%), m. p. 173—174° (Fromm and Schneider, *Annalen*, 1906, **348**, 161, record m. p. 173·5°); 1-*p*-chlorophenyl- (40 min., 40%), m. p. 179—180° (Fairfull, Lowe, and Peak, *J.*, 1952, 742, record m. p. 179—180°); 1-*p*-dimethylaminophenyl- (25 min., 39%), m. p. 159—160° (Found: N, 21·8; S, 25·6. Calc. for $C_{10}H_{14}N_4S_2$: N, 22·0; S, 25·2%) (Fromm and Weller, *Annalen*, 1908, **361**, 345, record m. p. 168—169°); 1-α-naphthyl- (1 hr., 44%), m. p. 194—195° (Found: C, 55·5; H, 4·0; N, 15·8. Calc. for $C_{12}H_{11}N_3S_2$: C, 55·2; H, 4·2; N, 16·0%) (Swaminathan and Guha, *loc. cit.*, record m. p. 246°); 1-β-naphthyl- (1·5 hr., 36%), m. p. 244—245° (*idem*, *ibid.*, record m. p. 245°); 1-methyl-1-phenyl- (1·5 hr., 55%), m. p. 156—157° (Fromm and Junius, *Ber.*, 1895, **28**, 1096, record m. p. 157°); and 1-ethyl-1-phenyl-, m. p. 128—129° (Found: N, 17·3. Calc. for $C_{10}H_{13}N_3S_2$: N, 17·6%) (Fromm and Baumhauer, *Annalen*, 1908, **361**, 319, record m. p. 119·5°).

p-Ethylsulphonylaniline, *p*-aminoacetanilide, *p*-aminoformanilide, *p*-phenylenediamine, *p*-nitroaniline, *p*-aminobenzonitrile, and ethyl *p*-aminobenzoate all failed to react with perthiocyanic acid.

2-Aminopyridine afforded *2-aminopyridine thiocyanate*, needles (from *n*-hexanol), m. p. 116—119° (Found: C, 47·4; H, 4·6. $C_6H_7N_3S$ requires C, 47·1; H, 4·6%), also prepared by

evaporating a solution of 2-aminopyridine and ammonium thiocyanate in methanol. Similarly, 3-aminopyridine afforded *3-aminopyridine thiocyanate*, m. p. 138—140° after repeated crystallisation from *iso*propanol (Found: N, 27·0. $C_6H_7N_3S$ requires N, 27·4%). *N*-(2-Diethylaminoethyl)aniline afforded an oily thiocyanate which regenerated the parent base when treated with aqueous sodium hydroxide.

(b) *From* iso*Thiocyanates and Sodium Cyanamide.*—(1) *Preparation of new* iso*thiocyanates.* *2-Pyridyl* iso*thiocyanate.* (i) From ammonium *N*-2-pyridyldithiocarbamate. Finely powdered 2-aminopyridine (225·6 g., 2·4 mols.) was added slowly to a mixture of concentrated aqueous ammonia (340 c.c., 5·2 mols.) and carbon disulphide (216 g., 2·84 mols.) at 0°. The turbid solution, which began to deposit yellow prisms after 2 hr., was stirred overnight at room temperature and the solid filtered off and washed with a little methanol and then with acetone. Evaporation of the mother-liquors yielded only 2-aminopyridine thiocyanate (154 g.), identified by mixed m. p. The yellow solid [61 g.; m. p. 96—97° (decomp.)] was unstable, decomposing on exposure to moist air or in a desiccator over sulphuric acid but it could be preserved in a stoppered bottle. It decomposed on attempted recrystallisation from methanol or aqueous ethanol with evolution of ammonia. It crystallised from dilute aqueous ammonia but its analysis (Found: N, 21·85. $C_6H_9N_3S_2$ requires N, 22·4%) indicated some loss of ammonia. Its identity as *ammonium* N-*2-pyridyldithiocarbamate* was confirmed by its acid hydrolysis to carbon disulphide, ammonia, and 2-aminopyridine, identified as its picrate, m. p. 221—222°.

The crude salt (25 g.) was suspended in dry toluene (200 c.c.) and a solution of carbonyl chloride (15·5 g., 1 mol.) in toluene (100 c.c.) added dropwise with stirring during 1·5 hr. at 0°, the colour of the solid progressively deepening. After being stirred overnight at room temperature, the solid was filtered off, washed with benzene, air-dried, and triturated with water (200 c.c.). The residue was filtered off and washed with water and finally with acetone (50 c.c.), affording *2-pyridyl* iso*thiocyanate* as a brick-red solid (15·4 g., 75%), m. p. 106—108°, raised to 110—111° by crystallisation from a large volume of acetone (Found: N, 20·4. $C_6H_4N_2S$ requires N, 20·6%). With aniline at 100° it afforded *N*-phenyl-*N'*-2-pyridylthiourea, m. p. and mixed m. p. 167—168°.

(ii) From triethylammonium *N*-2-pyridyldithiocarbamate. A mixture of 2-aminopyridine (6·27 g.), carbon disulphide (6 g., 1·2 mols.), triethylamine (111 g., 1·1 mols.), and absolute ethanol (5 c.c.) was kept for 2 days. The product which had separated was filtered off and washed with a little ethanol and with acetone, affording *triethylammonium* N-*2-pyridyldithiocarbamate* as yellow prisms (14·8 g.; 82%), m. p. 88—89° (decomp.) unchanged on recrystallisation from water containing a little triethylamine (Found: N, 15·5. $C_{12}H_{21}N_3S_2$ requires N, 15·5%).

Treatment of this salt with carbonyl chloride (1 mol.) as described above afforded 2-pyridyl *iso*thiocyanate (63·5%), m. p. 109—110°. Excess of carbonyl chloride gave *NN'*-di-2-pyridylthiourea as sole product.

3-Pyridyl iso*thiocyanate.* *Ammonium* N-*3-pyridyldithiocarbamate* was obtained as a pale yellow solid, m. p. 108° (Found: N, 22·1. $C_6H_9N_3S_2$ requires N, 22·4%), in 61% yield by the method described above for the 2-aminopyridine analogue. Treatment with carbonyl chloride (1 mol.) afforded a colourless precipitate and, by concentration of the toluene mother-liquor, a small quantity of an oil, b. p. 75—85°/2 mm. Redistillation at atmospheric pressure gave *3-pyridyl* iso*thiocyanate* (10%) as a pungent, colourless oil, b. p. 231—233° (Found: N, 19·8. $C_6H_4N_2S$ requires N, 20·6%). Its identity was confirmed by its condensation with aniline to give *N*-phenyl-*N'*-3-pyridylthiourea, m. p. 161—163° raised by admixture with authentic material of m. p. 163—164° (Camp, *Arch. Pharm.*, 1902, **240**, 356).

The colourless precipitate, after being washed with acetone, had m. p. 173—176°, not depressed by an authentic sample of *NN'-di-3-pyridylthiourea*, prisms (from ethanol), m. p. 178—179° (Found: N, 24·1. $C_{11}H_{10}N_4S$ requires N, 24·3%), prepared by condensing 3-pyridyl *iso*thiocyanate with 3-aminopyridine.

Triethylammonium N-*3-pyridyldithiocarbamate*, prisms (from acetone or ethanol–ether), m. p. 85—86° (Found: N, 15·2. $C_{12}H_{21}N_3S_2$ requires N, 15·5%), prepared in 92% yield as for the 2-aminopyridyl analogue, gave *NN'*-di-3-pyridylthiourea as the only isolatable product.

*9-Phenyl-2:7-diiso**thiocyanatophenanthridine.* A solution of 2:7-diamino-9-phenylphenanthridine (14·25 g.) in N-hydrochloric acid (100 c.c.) was vigorously stirred with a solution of thiocarbonyl chloride (10 c.c., 2·4 mols.) in chloroform (100 c.c.) while N-sodium hydroxide (200 c.c.) was added during 1 hr. The pale brown solid which separated was dissolved by the addition of further chloroform (600 c.c.), and the chloroform layer was dried ($MgSO_4$) and evaporated. The residual solid was extracted with hot benzene (100 c.c.), affording a residue of

9-*phenyl*-2 : 7-*diisothiocyanatophenanthridine* (13·7 g.) as pale brown needles, m. p. **235—236°** unchanged by crystallisation from a large volume of benzene (Found : N, 11·4. $C_{21}H_{11}N_3S_2$ requires N, 11·4%). A further crop (1·1 g.; m. p. 235—236°) was deposited by the hot benzene extract on cooling.

(2) *Preparation of dithiobiurets.* The following dithiobiurets were obtained by Hecht's method (*Ber.*, 1892, **25**, 749); 1-methyl- (33%), m. p. 157—158° (Hecht, *loc. cit.*, records m. p. 153°); 1-ethyl- (38%), m. p. 178—179° (*idem*, *ibid.*, records m. p. 175°); 1-n-*butyl*- (34%), plates (from aqueous methanol), m. p. 115—116° (Found : N, 21·8. $C_6H_{12}N_3S_2$ requires N, 22·0%); 1-2′-*pyridyl*- (22%), needles (from ethanol), m. p. 189—190° (Found : C, 39·5; H, 3·7; N, 26·2. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8; N, 26·4%); 1-3′-*pyridyl*- (35%), needles (from ethanol), m. p. 164—165° (Found : C, 39·8; H, 3·4; N, 26·4. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8; N, 26·4%); and 1-6′-*quinolyl*- (35%), needles (from aqueous ethanol), m. p. 180—181° (Found : C, 50·5; H, 3·9; N, 21·3. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8; N, 21·4%).

p-Ethoxycarbonylphenyl *iso*thiocyanate (Dyson, George, and Hunter, *J.*, 1927, 436) afforded a crude product which was purified by solution in dilute aqueous sodium hydroxide. Precipitation with hydrogen sulphide gave 1-(p-*ethoxycarbonylphenyl*)*dithiobiuret* (17·5%), m. p. 171—172° unchanged by crystallisation from aqueous ethanol (Found : N, 14·9. $C_{11}H_{13}O_2N_3S_2$ requires N, 14·85%). Acidification of the mother-liquor with acetic acid gave 1-p-*carboxyphenyldithiobiuret* (17%), m. p. 197—198° after crystallisation from aqueous ethanol (Found : N, 16·1. $C_9H_9O_2N_3S_2$ requires N, 16·5%). In one experiment, where the precipitate was left in contact with dilute hydrochloric acid overnight, the product was 3-p-*carboxyphenylimino*-5-*imino*-1 : 2 : 4-*dithiazolidine hydrochloride monohydrate* (12%), m. p. 237—238° after crystallisation from aqueous ethanol (Found : C, 35·0; H, 3·4; N, 13·3. $C_9H_5O_2N_3S_2,HCl,H_2O$ requires C, 35·1; H, 3·25; N, 13·6%). The same compound was prepared by oxidation of 1-*p*-carboxyphenyldithiobiuret with aqueous alcoholic ferric chloride.

1 : 4-Di*iso*thiocyanatobenzene (Billeter and Steiner, *Ber.*, 1887, **20**, 228) similarly afforded 1 : 4-*di*-(3-*thiocarbamoylthioureido*)*benzene* (37%), m. p. 192—193° (Found : N, 24·4. $C_{10}H_{12}N_6S_4$ requires N, 24·4%). 4 : 4′-Di*iso*thiocyanatodiphenyl (*idem*, *ibid.*) afforded 4 : 4′-*di*-(3-*thiocarbamoylthioureido*)*diphenyl* (47%), m. p. 256—257° (Found : C, 45·9; H, 3·8. $C_{16}H_{16}N_6S_4$ requires C, 45·7; H, 3·8%). 9-Phenyl-2 : 7-di*isothiocyanatophenanthridine afforded 9-*phenyl*-2 : 7-*di*-(3-*thiocarbamoylthioureido*)*phenanthridine monohydrate* (75%), m. p. 222—223° (Found : C, 51·5; H, 3·5; N, 18·1. $C_{23}H_{19}N_7S_4,H_2O$ requires C, 51·2; H, 3·9; N, 18·2%). All three bisdithiobiurets separated from aqueous pyridine as microcrystalline powders.

Ammonium and methyl dithiocarbamates, R·NH·CS·SR′.

R	R′	Yield (%)	M. p.	Formula	N (%) Found	N (%) Reqd.
2-Pyridyl-	$NHEt_3$			See p. 799		
2-*Pyridyl*-	Me	90	88—89°	$C_7H_8N_2S_2$	15·2	15·2
3-Pyridyl-	NH_4			See p. 799		
3-*Pyridyl*-	Me	96	133—135	$C_7H_8N_2S_2$	15·1	15·2
4-*iso*Quinolyl-	NH_4	80	119—120	$C_{10}H_{11}N_3S_2$	Not analysed	
4-iso*Quinolyl*-	Me	66	139—140	$C_{11}H_{10}N_2S_2$	11·9	12·0
5-*Quinolyl*-	NH_4	55	98—99	$C_{10}H_{11}N_3S_2$	17·5	17·7
5-*Quinolyl*-	Me	86	147—148	$C_{11}H_{10}N_2S_2$	12·1	12·0
6-*Quinolyl*-	NH_4	90	111—112	$C_{10}H_{11}N_3S_2$	17·5	17·7
6-*Quinolyl*-	Me	92	160—161	$C_{11}H_{10}N_2S_2$	12·0	12·0
8-*Quinolyl*-	NH_4	70	86—87	$C_{10}H_{11}N_3S_2$	17·8	17·7
8-*Quinolyl*-	Me	91	100—101	$C_{11}H_{10}N_2S_2$	12·0	12·0
p-*Acetamidophenyl*-	NH_4	73	212—220	$C_9H_{13}ON_3S_2$	17·0	17·3
p-*Acetamidophenyl*-	Me	93	139—140	$C_{10}H_{12}ON_2S_2$	11·8	11·7
p-*Propylphenyl*-	$NHEt_2$	83	92—93	$C_{10}H_{22}N_2S_2$	9·1	9·0
p-*Propylphenyl*-	Me	91	68—69	$C_{11}H_{15}NS_2$	6·4	6·2
p-*Butylphenyl*-	$NHEt_2$	83	91—92	$C_{17}H_{30}N_2S_2$	8·4	8·6
p-*Butylphenyl*-	Me	90	70—71	$C_{12}H_{17}NS_2$	6·0	5·9
2-*Thiazolyl*- *	$NHEt_2$	60	141—142	$C_{10}H_{15}N_3S_2$	14·9	15·2
2-*Thiazolyl*-	Me	83	184—185	$C_5H_6N_2S_2$	15·0	14·7

* Preparation carried out in acetone.

(c) *From Methyl Dithiocarbamates and Sodium Cyanamide.*—The required ammonium dithiocarbamates and methyl dithiocarbamates were made by conventional procedures and are listed in the Table. The only starting materials requiring comment are *p*-propyl- and *p*-butyl-aniline. These were prepared more conveniently than by recorded methods by the modified Wolff–

Kishner reduction (Herr, Whitmore, and Scheissler, *J. Amer. Chem. Soc.*, **1945**, **67**, 2061) of *p*-amino-propiophenone and -butyrophenone (Kunckell, *Ber.*, **1900**, **33**, 2641) in 58% and 83% yield respectively.

The following is a typical preparation of a dithiobiuret by this route. Methyl *N*-4-*iso*quinolyldithiocarbamate (14·2 g.) was heated under reflux for 24 hr. with a solution of sodium cyanamide, prepared by adding cyanamide (3·0 g.) to a solution of sodium (1·5 g.) in methanol (100 c.c.). (Longer heating is necessary if thiol evolution is sluggish.) The reaction mixture was evaporated to dryness on the steam-bath and the residual solid dissolved in water (100 c.c.) and filtered through kieselguhr. Ammonium chloride (3·6 g.) and concentrated ammonia solution (12 c.c.) were added and the solution was heated on the steam-bath in a stream of hydrogen sulphide. The solid which separated was filtered off at intervals and the filtrate re-treated until no further solid separated, affording a total of 14·0 g. (82%) of 1-4′-iso*quinolyldithiobiuret*, m. p. 184—185° (decomp.), unchanged by recrystallisation from a large volume of ethanol (Found: C, 50·6; H, 4·4; N, 21·5. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8; N, 21·4%).

The following dithiobiurets were obtained in a similar manner and crystallised from ethanol: 1-3′-pyridyl- (38%), m. p. and mixed m. p. 164—165°; 1-5′-*quinolyl*- (51%), m. p. 167—168° (Found: C, 50·0; H, 4·4. $C_{11}H_{10}N_4S_2$ requires C, 50·4; H, 3·8%); 1-p-*acetamidophenyl*- (71%), m. p. 190—191° (Found: C, 44·5; H, 4·5; N, 20·7. $C_{10}H_{13}ON_4S_2$ requires C, 44·8; H, 4·5; N, 20·8%); 1-p-*propylphenyl*- (63%), m. p. 160—161° (Found: C, 52·4; H, 5·9; N, 16·3. $C_{11}H_{15}N_3S_2$ requires C, 52·2; H, 5·9; N, 16·6%); and 1-p-*butylphenyl*- (35%), m. p. 158—159° (Found: N, 15·6. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

In two cases the intermediate *N*-cyanothiourea was isolated. Addition of ammonium chloride to the aqueous solution of the crude reaction product of the dithiocarbamate and sodium cyanamide afforded N-*cyano*-N′-2-*pyridylthiourea* (70%) as a yellow solid, m. p. 202—203° unchanged by recrystallisation from ethanol (Found: C, 47·2; H, 3·5; N, 31·0. $C_7H_6N_4S$ requires C, 47·2; H, 3·4; N, 31·4%). Methyl *N*-6-quinolyldithiocarbamate afforded in the same manner the cyano-derivative as its colourless *ammonium salt*, prisms (from dilute aqueous ammonia), m. p. 185—186° (Found: N, 28·3. $C_{11}H_{11}N_5S$ requires N, 28·6%), converted quantitatively into the yellow N-*cyano*-N′-6-*quinolylthiourea*, m. p. 180—181° (Found: N, 24·6. $C_{11}H_8N_4S$ requires N, 24·6%), by acidification of its aqueous solution with acetic acid. These cyano-derivatives were converted into the corresponding dithiobiurets in 82% and 72·5% yield respectively by addition of hydrogen sulphide in pyridine–triethylamine solution (Fairfull *et al.*, *loc. cit.*).

Methyl *N*-8-quinolyldithiocarbamate behaved abnormally, much decomposition occurring during the cyanamide condensation, and no dithiobiuret could be obtained. Methyl *N*-2-thiazolyldithiocarbamate afforded an unidentified yellow solid, m. p. 164—170°, also formed in the absence of cyanamide.

1 : 5-*Disubstituted dithiobiurets.*

The required thioureas were prepared (1) from the *iso*thiocyanate and ammonia or the appropriate amine or (2) from benzoyl *iso*thiocyanate and amine with subsequent hydrolysis of the *N*-benzoylthiourea (*Org. Synth.*, **28**, 89). The following new thioureas were obtained by the latter method: N′-*benzoyl*-N-2-*pyridyl*-, needles (from ethanol), m. p. 143—144° (Found: N, 16·4. $C_{13}H_{11}ON_3S$ requires N, 16·35%); N-2-*pyridyl*-, prisms (from ethanol), m. p. 147—148° (Found: N, 27·6. $C_6H_7N_3S$ requires N, 27·5%); N′-*benzoyl*-N-*methyl*-N-*phenyl*-, plates (from ethanol), m. p. 136—137° (Found: N, 10·4. $C_{15}H_{14}ON_2S$ requires N, 10·4%); N′-*benzoyl*-N-*phenyl*-N-*propyl*-, prisms (from ethanol), m. p. 126—127° (Found: N, 9·7. $C_{17}H_{18}ON_2S$ requires N, 9·4%); and N-*phenyl*-N-*propyl*-, plates (from benzene–light petroleum), m. p. 105° (Found: N, 14·5. $C_{10}H_{14}N_2S$ requires N, 14·4%). The last two *N*-benzoyl derivatives were resistant to hydrolysis and required heating under reflux for 2 hr.

By following the procedure of Curd *et al.* (*J.*, **1949**, 1739), the thioureas were converted into the *S*-ethyl*iso*thioureas and the latter, with or without intermediate isolation as their hydriodides, were condensed with the appropriate *iso*thiocyanate, and the resulting 2-ethyl-2-*iso*dithiobiurets were thiohydrolysed with ethanolic sodium hydrogen sulphide to the dithiobiurets. In this manner *NS*-diethyl*iso*thiourea and phenyl *iso*thiocyanate afforded 1 : 2-*diethyl*-5-*phenyl*-2-iso*dithiobiuret* (57%), prisms (from light petroleum), m. p. 93—94° (Found: N, 15·4. $C_{12}H_{17}N_3S_2$ requires N, 15·7%), and thence 1-*ethyl*-5-*phenyldithiobiuret* (87%), needles (from light petroleum–benzene), m. p. 131—132° (Found: N, 17·4. $C_{10}H_{13}N_3S_2$ requires N, 17·6%).

N-Butyl-*S*-ethyl*iso*thiourea and phenyl *iso*thiocyanate similarly afforded 1-butyl-2-ethyl-5-phenyl-2-*iso*dithiobiuret as an uncrystallisable oil, thiohydrolysed directly to 1-*butyl*-5-*phenyl*-

dithiobiuret (39%), needles (from light petroleum), m. p. 96—97° (Found: N, 15·4. $C_{12}H_{17}N_3S_2$ requires N, 15·7%).

S-Ethyl-*N*-phenyl*iso*thiourea and *p*-methoxyphenyl *iso*thiocyanate afforded **2-*ethyl*-5-p-*methoxyphenyl*-1-*phenyl*-2-iso*dithiobiuret*** (54%), prisms (from light petroleum), m. p. 106—107° (Found: N, 12·3. $C_{17}H_{19}ON_3S_2$ requires N, 12·2%), thiohydrolysed to **5-p-*methoxyphenyl*-1-*phenyldithiobiuret*** (53%), needles (from benzene–light petroleum), m. p. 138—139° (Found: N, 13·2. $C_{15}H_{15}ON_3S_2$ requires N, 13·2%).

S-*Ethyl*-N-p-***methoxyphenyl*isothiourea *hydriodide***, needles (from *iso*propanol–ether), m. p. 131—132° (Found: N, 8·3. $C_{10}H_{15}ON_2IS$ requires N, 8·3%), and *p*-methoxyphenyl *iso*thiocyanate afforded **2-*ethyl*-1 : 5-*di*-p-*methoxyphenyl*-2-iso*dithiobiuret*** (75%), prisms (from ethanol), m. p. 138—139° (Found: N, 11·2. $C_{18}H_{21}O_2N_3S_2$ requires N, 11·2%), thiohydrolysed to **1 : 5-*di*-p-*methoxyphenyldithiobiuret*** (51%), needles (from benzene–light petroleum), m. p. 131—132° (Found: N, 11·9. $C_{16}H_{17}O_2N_3S_2$ requires N, 12·1%).

S-*Ethyl*-N-*phenyl*-N-***propyl*isothiourea *hydriodide***, plates (from *iso*propanol), m. p. 153—154° (Found: N, 8·2. $C_{12}H_{19}N_2IS$ requires N, 8·0%), and ethyl *iso*thiocyanate afforded **2 : 5-*diethyl*-1-*phenyl*-1-*propyl*-2-iso*dithiobiuret*** (51%), needles (from light petroleum–benzene), m. p. 100—101° (Found: C, 57·9; H, 6·9; N, 13·9. $C_{15}H_{23}N_3S_2$ requires C, 58·3; H, 7·4; N, 13·6%). Thiohydrolysis (in pyridine–triethylamine) gave **5-*ethyl*-1-*phenyl*-1-*propyldithiobiuret*** (88%), needles (from light petroleum), m. p. 97—98° (Found: C, 55·4; H, 7·0; N, 14·8. $C_{13}H_{19}N_3S_2$ requires C, 55·5; H, 6·8; N, 15·0%).

S-*Ethyl*-N-***methyl*-N-*phenyl*isothiourea *hydriodide***, needles (from ethanol–ether), m. p. 137—138° (Found: N, 8·9. $C_{10}H_{15}N_2IS$ requires N, 8·7%), and ethyl *iso*thiocyanate afforded **2 : 5-*diethyl*-1-*methyl*-1-*phenyl*-2-iso*dithiobiuret*** (44%), prisms (from light petroleum–benzene), m. p. 81—82° (Found: C, 55·1; H, 6·7; N, 14·7. $C_{13}H_{19}N_3S_2$ requires C, 55·5; H, 6·8; N, 14·9%). Thiohydrolysis (in pyridine–triethylamine) gave **5-*ethyl*-1-*methyl*-1-*phenyldithiobiuret*** (87%), prisms (from light petroleum–benzene), m. p. 87—88° (Found: C, 51·9; H, 5·7; N, 16·5. $C_{11}H_{15}N_3S_2$ requires C, 52·1; H, 6·0; N, 16·6%).

Quaternary N-*derivatives.*

1-p-***Dimethylaminophenyldithiobiuret Methochloride.***—(i) *p*-Dimethylaminophenyl *iso*thiocyanate was prepared in improved yield (47% instead of 13%) by a modification of the Organic Syntheses' method (Coll. Vol. I, 1st Edn., 447). Instead of steam-distillation of the product, the reaction mixture was filtered and the *iso*thiocyanate extracted from the cake with hot acetone (3 × 300 c.c. on 0·2-molar scale). The combined extracts were evaporated under reduced pressure. The resulting colourless solid, after being pressed on a filter and washed with water, had m. p. 68—70°.

A solution of the *iso*thiocyanate (16·5 g.) in dry acetone (30 c.c.) and methyl iodide (10 c.c.) was kept at 0°. Over a period of 17 days, successive crops (26·1 g.) of **N-*trimethyl*-p-iso*thiocyanatoanilinium iodide*** were obtained, having m. p. 190° (decomp.) (Found: N, 8·9. $C_{10}H_{13}N_2IS$ requires N, 8·8%). Condensation of this in the usual manner with sodium cyanamide and thiohydration of the product afforded a precipitate of the crude dithiobiuret. This dissolved in warm dilute hydrochloric acid, the solution soon depositing **1-p-*dimethylaminophenyldithiobiuret methochloride*** (10·5%) as needles, m. p. 192° (decomp.) after recrystallisation from water (Found: C, 43·7; H, 5·3; N, 18·4. $C_{11}H_{17}N_4ClS_2$ requires C, 43·4; H, 5·6; N, 18·4%).

(ii) **1-p-*Dimethylaminophenyl*-2 : 4-*dimethyldi*isodithiobiuret** was obtained in 46% yield by shaking a solution of the dithiobiuret in N-sodium hydroxide (2 equivs.) with methyl iodide (2 mols.) for 30 min. It crystallised from ethanol in needles, m. p. 105—106° (Found: C, 51·4; H, 6·9; N, 19·7. $C_{12}H_{18}N_4S_2$ requires C, 51·1; H, 6·4; N, 19·8%).

When this compound was kept for 2 days in acetone solution containing methyl iodide (1 mol.), the ***methiodide*** (80%) was obtained as a colourless solid, m. p. 185—186° (Found: C, 36·7; H, 5·0; N, 12·9. $C_{13}H_{21}N_4IS_2$ requires C, 36·8; H, 5·0; N, 13·2%).

The methiodide (0·51 g.) was heated under reflux for 1½ hr. in a stream of hydrogen sulphide with ethanolic sodium hydrogen sulphide, prepared by saturating a solution of sodium (0·08 g.) in ethanol (20 c.c.). The white precipitate which formed was isolated and dissolved in N-hydrochloric acid (10 c.c.), from which the dithiobiuret methochloride (0·25 g.) crystallised in needles, m. p. (after recrystallisation from dilute ammonium chloride solution) 192° (decomp.) undepressed by the material described above.

1-6′-*Quinolyldithiobiuret* 1′-*Methochloride.*—(i) 6-*iso*Thiocyanatoquinoline (Gulland and

Macey, *J.*, 1949, 1249) similarly afforded *1-methyl-6-isothiocyanotoquinolinium iodide* (82%) as red needles, m. p. 237—238° (Found: N, 8·3. $C_{11}H_9N_2IS$ requires N, 8·5%).

Condensation with sodium cyanamide and thiohydrolysis gave a product from which *1-6′-quinolyldithiobiuret 1′-methochloride* (17%) was obtained on treatment with dilute hydrochloric acid as buff plates, m. p. 219—220° (Found: C, 46·1; H, 4·4; N, 17·6. $C_{13}H_{13}N_4ClS_2$ requires C, 46·1; H, 4·2; N, 17·9%).

(ii) 1-6′-Quinolyldithiobiuret was converted into *2 : 4-dimethyl-1-6′-quinolyldiisodithiobiuret* (54%), plates (from aqueous ethanol), m. p. 152—153° (Found: N, 19·2. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Quaternisation in acetophenone at 70° afforded the *methiodide* (80%), m. p. 174° (Found: N, 13·1. $C_{14}H_{17}N_4IS_2$ requires N, 13·0%). Thiohydrolysis in pyridine–triethylamine and treatment with hydrochloric acid gave 1-6′-quinolyldithiobiuret 1′-methochloride (12%), identical in m. p. and mixed m. p. with the above compound.

(iii) *N*-Cyano-*N*′-6-quinolylthiourea was methylated as usual to give *N-cyano-S-methyl-N′-6-quinolylisothiourea* (80%), plates (from ethanol), m. p. 205—206° (Found: N, 22·9. $C_{12}H_{10}N_4S$ requires N, 23·1%). Quaternisation of this in acetophenone at 70° furnished the *methiodide* (89%), m. p. 218—219° (Found: N, 14·3. $C_{13}H_{13}N_4IS$ requires N, 14·6%). Thiohydrolysis as in (ii) and treatment with hydrochloric acid afforded the same compound in 8% yield.

1-3′-Pyridyldithiobiuret 1′-Methochloride.—1-3′-Pyridyldithiobiuret afforded *2 : 4-dimethyl-1-3′-pyridyldiisodithiobiuret* (51%), m. p. 126—127° (Found: C, 45·1; H, 5·1; N, 23·4. $C_9H_{12}N_4S_2$ requires C, 45·0; H, 5·0; N, 23·3%). Quaternisation in acetone gave the *methiodide* (90%), m. p. 192—193° (Found: C, 31·4; H, 4·0; N, 14·7. $C_{10}H_{15}N_4IS_2$ requires C, 31·4; H, 3·9; N, 14·7%). Thiohydrolysis with ethanolic sodium hydrogen sulphide and treatment with hydrochloric acid gave *1-3′-pyridyldithiobiuret methochloride monohydrate* (65%), needles (from dilute hydrochloric acid), m. p. 181—182° (Found: C, 34·2; H, 4·5; N, 20·0. $C_8H_{11}N_4ClS_2,H_2O$ requires C, 34·2; H, 4·6; N, 20·0%). If its aqueous solution (pH 4) was adjusted to *ca.* pH 7, *anhydro-1-3′-pyridyldithiobiuret methohydroxide* separated as prisms, m. p. 193—194° (Found: C, 42·9; H, 4·2; N, 24·6. $C_8H_{10}N_4S_2$ requires C, 42·5; H, 4·4; N, 24·8%).

1-4′-isoQuinolyldithiobiuret 2′-Methochloride.—1-4′-*iso*Quinolyldithiobiuret afforded *2 : 4-dimethyl-1-4′-isoquinolyldiisodithiobiuret* (82%), prisms (from ethanol), m. p. 194—195° (Found: N, 19·3. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Quaternisation in acetophenone at 70° gave the *methiodide* (85%), m. p. 199—200° (Found: N, 12·9. $C_{14}H_{17}N_4IS_2$ requires N, 13·0%). Thiohydrolysis in ethanolic sodium hydrogen sulphide or pyridine–triethylamine suspension for 4 hr. gave the starting material as its *methochloride*, m. p. 195—196° (Found: N, 16·8. $C_{14}H_{17}N_4ClS_2$ requires N, 16·5%), identified by reconversion with aqueous sodium iodide into the methiodide, m. p. and mixed m. p. 198—200°. Thiohydrolysis by the latter method for 40 hr. and treatment of the product with aqueous hydrochloric acid gave *1-4′-isoquinolyldithiobiuret methochloride* (73%), needles (from water), m. p. 194—195° (Found: C, 46·1; H, 4·3; N, 17·7. $C_{13}H_{13}N_4ClS_2$ requires C, 46·2; H, 4·2; N, 17·9%).

Attempted Preparation of 1-2′-Pyridyldithiobiuret 1′-Methochloride.—2-Pyridyl *iso*thiocyanate reacted readily with methyl iodide in acetone solution to give a *compound* of unknown structure as orange needles, m. p. 175° (decomp.) (Found: C, 37·8; H, 2·75; N, 13·5. $C_{13}H_{11}N_4IS_2$ requires C, 37·7; H, 2·7; N, 13·5%), evidently formed by the combination of two molecules of the *iso*thiocyanate with one of methyl iodide.

Attempted dimethylation of 1-2′-pyridyldithiobiuret under the usual conditions afforded, with loss of methanethiol, *N-cyano-S-methyl-N′-2-pyridylisothiourea hydriodide* (72%), needles (from ethanol), m. p. 237° (decomp.) (Found: C, 30·0; H, 2·9; N, 17·5. $C_8H_9N_4IS$ requires C, 30·0; H, 2·8; N, 17·5%). Its identity was confirmed by the methylation of *N*-cyano-*N*′-2-pyridylthiourea to give *N-cyano-S-methyl-N′-2-pyridylisothiourea* (80%), pale yellow needles (from light petroleum), m. p. 127—128° (Found: C, 50·4; H, 4·25; N, 28·8. $C_8H_8N_4S$ requires C, 50·0; H, 4·2; N, 29·2%), which afforded the above hydriodide when hydriodic acid was added to its solution in methanol.

Attempted Preparation of 1-5′-Quinolyldithiobiuret Methochloride.—1-5′-Quinolyldithiobiuret afforded *2 : 4-dimethyl-1-5′-quinolyldiisodithiobiuret*, prisms (from ethanol), m. p. 181—182° (Found: N, 19·1. $C_{13}H_{14}N_4S_2$ requires N, 19·3%). Attempted quaternisation failed under a variety of conditions.

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Dithiobiurets. Part II. Some Cyclic Derivatives.*

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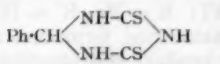
A number of cyclic dithiobiuret derivatives have been prepared for test as trypanocidal agents. The condensation products of dithiobiurets with aldehydes or ketones have been shown to be triazine derivatives, and not diaza*cyclo*butane derivatives as postulated by Fromm and his collaborators.

In continuation of our examination of dithiobiurets as potential trypanocidal compounds (see Part I *) we prepared a number of cyclic derivatives obtained by the condensation of dithiobiurets with aldehydes or ketones. This reaction was first observed by Fromm (*Annalen*, 1893, **275**, 20) who showed that under the influence of dry hydrogen chloride 1-phenyldithiobiuret condensed with acetone or benzaldehyde, with the elimination of water, to give compounds which he generically called "keturets" and "aldurets" respectively. Brodski (*Monatsh.*, 1887, **8**, 27) had earlier prepared a compound of this type indirectly by fusion of a mixture of benzaldehyde and ammonium thiocyanate and had ascribed to it the structure (I). A repetition of Brodski's work showed that the condensation product of dithiobiuret and benzaldehyde was in fact identical with his product. It was also identical with the product obtained by Foye and Hefferren (*J. Amer. Pharm. Assoc.*, 1953, **42**, 31) by heating dithiobiuret and benzaldehyde in acetic acid. These authors assumed the structure (II) without evidence.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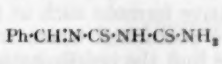
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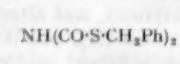
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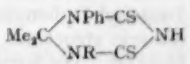
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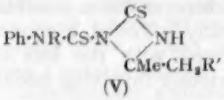
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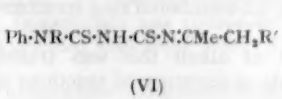
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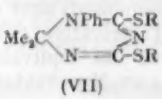
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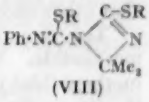
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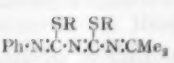
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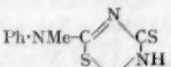
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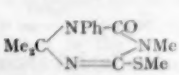
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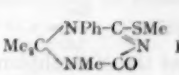
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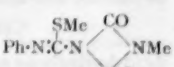
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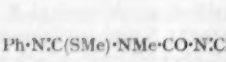
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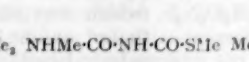
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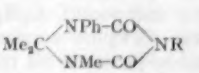
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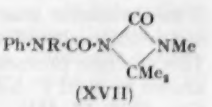
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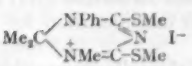
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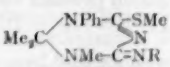
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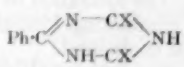
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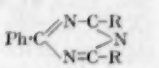

(XXI)

Compounds of this type seemed of potential interest since they could conceivably be formed *in vivo* from dithiobiurets and natural carbonyl constituents of the host, and might constitute the actual therapeutic agents. A number of such compounds were therefore prepared (see Table in Experimental) from dithiobiurets and a variety of carbonyl compounds. For reasons which appear below, they are formulated as hexahydrotriazine derivatives, a structure originally considered but rejected by Fromm (*loc. cit.*). Fromm's method of preparation proved generally satisfactory provided some ethanol was added as

* Part I, preceding paper.

a flux. Boron trifluoride–acetic acid complex was also found to be a satisfactory condensing agent.

The structure of the " aldurets " and " keturets " has not been rigidly proved. Fromm (*loc. cit.*) showed that benzylation of the condensation product of 1-phenyldithiobiuret and acetone gave a di-*S*-benzyl derivative since acid hydrolysis afforded dibenzyl iminodithiolcarboxylate (III). The thiocarbonyl groups are therefore not involved in the condensation and the possible structures are reduced to (IV, V, or VI; R = R′ = H), the alternative four-membered ring structure involving $N_{(1)}$ and $N_{(3)}$ being excluded by the formation of the di-*S*-benzyl derivative. Fromm regarded the second of these as the most probable for the following reasons. Of the corresponding structures (VII, VIII, and IX; R = CH_2Ph) for the dibenzyl derivative, Fromm regarded only (VIII; R = CH_2Ph) as likely to give rise to (III) because of the disposition of the carboimide linkages. The formation from 1-methyl-1-phenyldithiobiuret and acetone of an apparently similar " keturet " (Fromm and Junius, *Ber.*, 1895, **28**, 1096, 1102) was regarded as definitely excluding structure (IV; R = H) since such a structure is impossible where, as in this case, the phenylimino-group is blocked. Further evidence against structure (VI; R = R′ = H) was later provided by the observation (Fromm and Philippe, *Ber.*, 1899, **32**, 835) that the " keturet " from 1-phenyldithiobiuret and ethyl acetoacetate could be hydrolysed to the corresponding acid which showed no tendency to cyclodehydration. This was regarded as improbable for the structure (VI; R = H, R′ = CO_2H) but not unlikely for the structure (V; R = H, R′ = CO_2H).

This evidence appeared to us to be inconclusive and it seemed improbable for steric reasons that a diaz*ocyclo*butane ring would be formed in preference to a six-membered ring. There is no evidence for the structure (V; R = Me, R′ = H) for the " keturet " from 1-methyl-1-phenyldithiobiuret, and alternative formulæ such as (VI; R = Me, R′ = H), dimeric structures, or even (X), might be postulated where triazine ring formation is blocked. We have now obtained evidence that the condensation product of 1-phenyldithiobiuret and acetone has the structure (IV; R = H) and it appears reasonable to assume that other such compounds have the six-membered ring structure wherever this is possible.

The dimethyl derivative (VII, VIII, or IX; R = Me) readily afforded a monomethiodide. With one equivalent of alkali this was transformed with the loss of methanethiol into an *N*-methylamide, a sequence of reactions obviously involving one of the thioimidic groups :

$$\cdot C(SMe){:}N\cdot \xrightarrow{MeI} \cdot C(SMe){:}\overset{+}{N}Me\cdot\}I^- \xrightarrow{NaOH} \cdot CO\cdot NMe\cdot + NaI + MeSH$$

Acid hydrolysis of the *N*-methylamide afforded aniline and not *N*-methylaniline, showing that the *N*-phenyl group was not involved. The four possible structures for the *N*-methylamide are therefore (XI)—(XIV). A second major product of acid hydrolysis of the *N*-methylamide was a compound, $C_4H_8O_2N_2S$, which was identified as *N*-methyl-*N*′-methylthiocarbonylurea (XV) by conversion with hot aniline into 1 : 5-diphenylbiuret. This reaction presumably proceeds *via* the intermediate 1-methyl-5-phenylbiuret which is known to yield 1 : 5-diphenylbiuret under the same conditions (Gatewood, *J. Amer. Chem. Soc.*, 1925, **47**, 411). The formation of this fission product eliminates structures (XI) and (XIV), thereby also eliminating formula (VI; R = R′ = H) from consideration for the structure of the parent compound.

A choice between structures (XII) and (XIII) was possible from the following considerations. The *N*-methylamide (XII or XIII) afforded a methiodide, although with difficulty and in poor yield, quaternisation evidently involving the second thioimidic group since with alkali the quaternary system underwent the same transformation as in the previous case to an *N*-methylamide grouping to give (XVI or XVII; R = Me). The same compound was obtained more readily by oxidation of the *N*-methylamide (XII or XIII) with hydrogen peroxide, whereby the methylthio-group was eliminated to give the compound (XVI or XVII; R = H). Methylation of the latter with sodium hydroxide and methyl iodide gave (XVI or XVII; R = Me). That this compound was an *N*- and not an *O*-methyl derivative was confirmed by its low methoxyl content by Zeisel determination. Both the methiodide and the compound (XVI or XVII; R = Me) gave aniline

and not *N*-methylaniline on acid hydrolysis. Structures (XVII; R = Me) and hence (XIII) are therefore eliminated. These observations also provide additional evidence against structure (XIV).

The parent compound can therefore unequivocally be assigned the hexahydrotriazine structure (IV; R = H) (or one of its tautomeric equivalents). The methiodide of the di-*S*-methyl derivative (VII; R = Me) is therefore (XVIII). In addition to its behaviour with alkali, it undergoes the expected reactions (cf. Peak and Stansfield, *J.*, **1952**, 4067) with ammonia, aniline, and thiosemicarbazide to give respectively the imino-derivative (XIX; R = H), the phenylimino-derivative (XIX; R = Ph), and the thiosemicarbazono-derivative (XIX; R = ·NH·CS·NH_2), and it can be thiohydrolysed to (IV; R = Me).

As a further type of cyclic dithiobiuret, the tetrahydrotriazine (XX; X = S) was prepared. 2 : 4-Dihydroxy-6-phenyl-1 : 3 : 5-triazine (XXI; R = OH) [or its tautomeride (XX; X = O)] (Adams, Ragg, Peters, Kaiser, Sperry, and Thurston, *J. Org. Chem.*, **1952**, **17**, 1145) was converted with phosphorus oxychloride into the dichlorotriazine (XXI; R = Cl), a compound previously obtained by Ostrogovich (*Chem. Ztg.*, **1912**, **36**, 739) by the action of phenylmagnesium bromide on cyanuric chloride. Treatment of this compound with potassium hydrogen sulphide afforded the required compound (XX; X = S). The same compound could also be obtained by the successive action of benzoyl chloride and pyridine on dithiobiuret, presumably through the intermediate formation of 1-benzoyldithiobiuret. Unsuccessful methods tried were the fusion of benzamidine with perthiocyanic acid which afforded benzamidinium thiocyanate as sole product, and condensation of dithiobiuret with orthocarboxylic esters which afforded only alkyl*iso*dithiobiurets.

The majority of the compounds described were tested for trypanocidal activity with negative results.

Experimental

Preparation of Hexahydro-4 : 6-thiono-1 : 3 : 5-triazines.—A mixture of the dithiobiuret and the aldehyde or ketone (10% excess) was suspended in ethanol (5 parts) and saturated with dry hydrogen chloride. The solid usually dissolved completely, more ethanol being used if this did not occur. After 30 min., the mixture was poured into an excess of N-sodium hydroxide, warmed to 50°, filtered, and acidified with acetic acid. The solid was collected and crystallised from a suitable solvent.

Alternatively, a mixture of equimolecular quantities of the dithiobiuret, aldehyde (or ketone), and boron fluoride–acetic acid complex was heated on the steam-bath for 15 min. and worked up as above.

The compounds so prepared are listed in the accompanying Table. No condensation products could be obtained from phenyldithiobiuret and pyruvic acid, crotonaldehyde, or benzoquinone.

1 : 2-*Dihydro*-2 : 2-*dimethyl*-4 : 6-*dimethylthio*-1 : 3 : 5-*triazine* 3-*Methiodide* (XVIII).—1 : 2-Dihydro-2 : 2-dimethyl-4 : 6-dimethylthio-1 : 3 : 5-triazine (23 g.) (Underwood and Dains, *Univ. Kansas Sci. Bull.*, **1936**, **24**, 5) was heated under reflux overnight with acetone (100 c.c.) and methyl iodide (16 c.c.). On cooling and seeding, the *methiodide* (32 g.) crystallised in needles, m. p. 184—186° (decomp.), unchanged by recrystallisation from methanol–ether (Found: N, 10·1. $C_{14}H_{20}N_3IS_2$ requires N, 10·0%).

Reactions of the Methiodide.—(a) *With hydrogen sulphide.* A solution of the methiodide (5·25 g.) in pyridine (50 c.c.) and triethylamine (5·1 g.) was saturated with dry hydrogen sulphide for 2 hr. The mixture was poured into water and the solid (3·17 g.) collected. Crystallisation from butanol or pyridine afforded *hexahydro*-2 : 2 : 3-*trimethyl*-1-*phenyl*-4 : 6-*thiono*-1 : 3 : 5-*triazine* (IV; R = Me) as plates, m. p. 244—245° (Found: C, 54·2; H, 6·1; N, 15·9. $C_{12}H_{15}N_3S_2$ requires C, 54·3; H, 5·6; N, 15·8%).

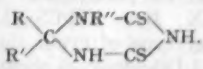
(b) *With thiosemicarbazide.* The methiodide (1·05 g.) was shaken with thiosemicarbazide (0·23 g.), pyridine (5 c.c.), and diethylamine (1 c.c.). There was an immediate smell of thiol, and dissolution was complete in a few minutes. The product, *tetrahydro*-2 : 2 : 3-*trimethyl*-6-*methylthio*-1-*phenyl*-4-*thiosemicarbazono*-1 : 3 : 5-*triazine* (XIX; R = NH·CS·NH_2), obtained by pouring the mixture into water was a colourless solid (0·65 g.), m. p. 191—192° unchanged by recrystallisation from ethanol (Found: N, 24·8. $C_{14}H_{20}N_6S_3$ requires N, 25·0%).

(c) *With ammonia.* The methiodide (0·5 g.) was shaken with ethanolic ammonia (4 c.c. of 2·4N) until dissolution was complete and then kept for 4 hr. The ethanol was then removed in

a current of air and the residue triturated with water (3 c.c.). The product, tetrahydro-4-imino-2 : 2 : 3-trimethyl-6-methylthio-1-phenyl-1 : 3 : 5-triazine (XIX; R = H), separated as its *hydriodide monohydrate* (0·33 g.), m. p. 110—112° raised to 112—114° by recrystallisation from water (Found: C, 38·4; H, 5·0; N, 13·7. $C_{12}H_{19}N_4IS,H_2O$ requires C, 38·2; H, 5·15; N, 13·7%). A solution of this (0·5 g.) in hot water (5 c.c.) treated with N-sodium hydroxide (1 equiv.) deposited, on cooling, a colourless oil which solidified. This proved to be unchanged material.

(d) *With aniline.* A mixture of methiodide (5·0 g.), pyridine (12 c.c.), aniline (1·09 c.c.; 1 mol.), and diethylamine (1·38 c.c.; 1·1 mol.) was kept for 60 hr., dissolution then being

Hexahydro-4 : 6-thiono-1 : 3 : 5-triazines,



Compound	R	R′	R″	Solvent [a]	M. p.	Formula	N (%) Found	N (%) Reqd.
(1) 2 : 2-*Dimethyl-* ...	Me	Me	H	A	282—283°	$C_5H_9N_3S_2$	24·35	24·0
(2) 2-Phenyl-[b]	Ph	H	H	B	243—244	$C_9H_9N_3S_2$	18·95	18·8
(3) 2-*p*-Methoxyphenyl-[c]	*p*-MeO·C_6H_4	H	H	B	236—237	$C_{10}H_{11}ON_3S_2$	16·55	16·6
(4) 2-*p*-Acetamidophenyl-[d]	*p*-NHAc·C_6H_4	H	H	C	252—253	$C_{11}H_{12}ON_4S_2$	20·1	20·0
(5) 2-*Methyl*-2-*phenyl-*	Ph	Me	H	C	281—282	$C_{10}H_{11}N_3S_2$	17·4	17·7
(6) 2-p-*Chlorophenyl*-1-*phenyl-*	*p*-C_6H_4Cl	H	Ph	B	215—216	$C_{15}H_{12}N_3ClS_2$	12·5	12·6
(7) 2-p-*Methoxyphenyl*-1-*phenyl-* ...	*p*-C_6H_4·OMe	H	Ph	D	197—198	$C_{16}H_{15}ON_3S_2$	13·0	12·8
(8) 2-m-*Nitrophenyl*-1-*phenyl-*	*m*-C_6H_4·NO_2	H	Ph	B	210—211	$C_{15}H_{12}O_2N_4S_2$	16·2	16·3
(9) 2-p-*Acetamidophenyl*-1-*phenyl-*	*p*-C_6H_4·NHAc	H	Ph	B	219—220	$C_{17}H_{16}ON_4S_2$	15·9	15·7
(10) 2-p-*Aminophenyl*-1-*phenyl-*[e]	*p*-C_6H_4·NH_2	H	Ph	B	203—204	$C_{15}H_{14}N_4S_2$	17·5	17·8
(11) 2-*Methyl*-1 : 2-*diphenyl-*	Ph	Me	Ph	B	198—198·5	$C_{16}H_{15}N_3S_2$	13·2	13·4
(12) 1-*Phenyl*-2-*styryl-*	Ph·CH:CH	H	Ph	B	201—202	$C_{17}H_{15}N_3S_2$	12·9	12·9
(13) 1-p-*Carboxyphenyl*-2-*phenyl-* ...	Ph	H	*p*-C_6H_4·CO_2H	A	231—232	$C_{16}H_{13}O_2N_3S_2$	12·4	12·2
(14) 2-Carboxymethyl-2-methyl-[f]	·CH_2·CO_2H	Me	Ph	B	208	$C_{13}H_{15}O_2N_3S_2$	14·3	14·2

[a] A = EtOH; B = BuOH; C = pyridine–ether; D = chlorobenzene. [b] Brodski (*loc. cit.*) records m. p. 237°. Foye and Hefferren (*loc. cit.*) record m. p. 236—238°. Both products were undepressed in m. p. by our product. [c] *Idem, ibid.*, record m. p. 239—240°. [d] *Idem, ibid.*, record m. p. 249—250°. [e] Prepared by alkaline hydrolysis of the foregoing compound. [f] Fromm and Philippe (*loc. cit.*) record m. p. 214—216°.

complete. Dilution with water gave an oil which soon crystallised (2·27 g.; m. p. 151—152°). Recrystallisation from light petroleum or methanol afforded pure 4-*phenyliminotetrahydro*-2 : 2 : 3-*trimethyl*-6-*methylthio*-1-*phenyl*-1 : 3 : 5-*triazine* (XIX; R = Ph), m. p. 153—154° (Found: N, 16·5. $C_{18}H_{23}N_4S$ requires N, 16·6%).

(e) *With sodium hydroxide.* N-Sodium hydroxide (102 c.c.; 1 equiv.) was added to a solution of the methiodide (42·6 g.) in methanol (70 c.c.), thiol being immediately liberated. After 2½ hr. the methanol was evaporated under reduced pressure to crystallisation point. A first crop (23·5 g.; m. p. 145—147°) was thus obtained and a second crop (0·48 g.; m. p. 142°) by further concentration. Recrystallisation from acetone afforded *tetrahydro*-2 : 2 : 3-*trimethyl*-6-*methylthio*-4-*oxo*-1-*phenyl*-1 : 3 : 5-*triazine* (XII) (15·3 g.), m. p. 156—157° (Found: C, 59·3; H, 6·5; N, 15·9. $C_{13}H_{17}ON_3S$ requires C, 59·3; H, 6·5; N, 16·0%). The *picrate* separated from ethanol in prisms, m. p. 161—161·5° (Found: C, 46·75; H, 4·0; N, 17·3. $C_{19}H_{20}O_8N_6S$ requires C, 46·35; H, 4·05; N, 17·1%).

Hydrolysis of Tetrahydro-2 : 2 : 3-*trimethyl*-4-*oxo*-1-*phenyl*-6-*methylthio*-1 : 3 : 5-*triazine* (XII). —This compound (1·0 g.) was heated on the steam-bath with 5N-hydrochloric acid (5 c.c.) for 3 hr., methanethiol being evolved. On cooling, a solid crystallised in plates. After filtration the mother-liquor was diluted with water, and sodium bromide (4 g.) was added and then aqueous sodium bromate until free bromine was detectable. The precipitated 2 : 4 : 6-tribromoaniline (1·17 g., 93·5%) had m. p. and mixed m. p. 116—117°.

Recrystallisation of the crystalline hydrolysis product (0·28 g.) from light petroleum and from ethyl acetate afforded N-*methyl*-N′-*methylthiocarbonylurea* (XV) as plates, m. p. 146—147°

(Found: C, 32·7; H, 5·9; N, 19·1. $C_4H_8O_2N_2S$ requires C, 32·4; H, 5·4; N, 18·9%). It was soluble in dilute aqueous sodium hydroxide but not in sodium carbonate, and its sulphur was not present as thiono-sulphur (negative sodium plumbite test). When warmed for a few minutes with an excess of aniline just below its b. p., it afforded 1 : 5-diphenylbiuret, which after repeated crystallisation from ethanol had m. p. 209—210° undepressed by authentic material prepared from phenylurea and phenyl *iso*cyanate (Kuhn and Hentschel, *Ber.*, 1888, **21**, 504).

Tetrahydro-2 : 2 : 3-trimethyl-6-methylthio-4-oxo-1-phenyl-1 : 3 : 5-triazine 5-Methiodide.—The foregoing material (2·08 g.) was heated with methyl iodide (20 c.c.) in a sealed tube at 70° for 96 hr. A small amount of needles (0·08 g.; m. p. >250°) was filtered off and identified as dimethylammonium iodide by conversion into the picrate, m. p. and mixed m. p. 158—160°. The mother-liquor was evaporated *in vacuo* and the residue was extracted with hot benzene (15 c.c.). Crystallisation of the benzene-insoluble fraction afforded the *5-methiodide* as plates, m. p. 127—128° (Found: C, 41·3; H, 5·0. $C_{14}H_{20}ON_3IS$ requires C, 41·5; H, 4·95%).

The methiodide (0·22 g.) was heated overnight under reflux with concentrated hydrochloric acid (5 c.c.). The solution was evaporated to dryness *in vacuo*, and the residue basified with 5N-sodium hydroxide and extracted with ether. The dried extract was evaporated after the addition of acetic anhydride (0·2 c.c.). Water (0·2 c.c.) was added to the residue whereupon acetanilide (0·016 g.) crystallised, having m. p. and mixed m. p. 112—113°. Evaporation of the mother-liquor furnished, after crystallisation from light petroleum, a further 0·012 g., making a total of 0·028 g. (35%).

Hexahydro-2 : 2 : 3-trimethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine (XVI; R = H).—Tetrahydro-2 : 2 : 3-trimethyl-6-methylthio-4-oxo-1-phenyl-1 : 3 : 5-triazine (3·40 g.) was dissolved in glacial acetic acid (13·5 c.c.) and hydrogen peroxide (3·4 c.c of 100-vol.) was added with water-cooling. After 12 hr. the solution was diluted with water and made alkaline with sodium carbonate. The crystalline precipitate was collected and recrystallised from ethanol, affording *hexahydro-2 : 2 : 3-trimethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine* as needles, m. p. 248—249° raised to 251—252° by further recrystallisation (Found: C, 61·8; H, 6·5; N, 18·1. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·4; N, 18·0%). The compound was soluble in dilute aqueous sodium hydroxide but not in sodium carbonate.

Hexahydro-2 : 2 : 3 : 5-tetramethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine (XVI; R = Me).—(*a*) N-Sodium hydroxide (10 c.c., 2 equivs.) was added to a suspension of the foregoing compound (1·13 g.) in methanol (17·5 c.c.), a clear solution resulting. Excess of methyl iodide (1·0 c.c.) was added and the mixture kept 12 hr. after which it was neutral. The methanol was removed in a current of air, the product (0·98 g.) crystallising in plates, m. p. 138—140°. Repeated recrystallisation from light petroleum (b. p. 100—120°) afforded *hexahydro-2 : 2 : 3 : 5-tetramethyl-4 : 6-dioxo-1-phenyl-1 : 3 : 5-triazine* as needles, m. p. 146—147° with sintering at 141° [Found: C, 63·4; H, 7·1; OMe, 0·30, 0·25. $C_{13}H_{17}O_2N_3$ requires C, 63·1; H, 6·9; OMe, 0% (6·0% for 1OMe)]. It was feebly basic, insoluble in N- but soluble in 5N-hydrochloric acid from which it could be recovered unchanged after 12 hr.

(*b*) The foregoing 5-methiodide (0·15 g.) was dissolved in warm water (3 c.c.), the odour of methanethiol becoming immediately apparent. N-Sodium hydroxide (0·37 c.c., 1 equiv.) was then added. The solution was cooled and the crystalline product (0·06 g.) filtered off. Recrystallisation from light petroleum afforded the above compound (XVI; R = Me) as needles, m. p. and mixed m. p. 146—147° (Found: C, 62·8, 63·2; H, 6·7, 6·9%).

The compound (0·4 g.) was heated under reflux with 48% hydrobromic acid (5 c.c.), and the solution evaporated to dryness. The crystalline residue was basified with sodium hydroxide and steam-distilled and the steam-distillate extracted with ether. The extract was dried and treated for 1 hr. with pyridine (0·19 g.) and benzoyl chloride (0·25 g.). The solution was evaporated *in vacuo* and the residue triturated with water, affording benzanilide (0·24 g., 75%), m. p. and mixed m. p. 160—161°.

Tetrahydro-2-phenyl-4 : 6-dithiono-1 : 3 : 5-triazine (XX; X = S).—(*a*) 2 : 4-Dihydroxy-6-phenyl-1 : 3 : 5-triazine (Adams *et al.*, *loc. cit.*) (120 g.) was heated under reflux with phosphorus oxychloride (60 c.c.) for 1½ hr. The clear solution was poured on ice, and the 2 : 4-dichloro-6-phenyl-1 : 3 : 5-triazine (XXI; R = Cl) was isolated and crystallised from ethanol (8·4 g.; m. p. 119—120°) (Ostrogovich, *loc. cit.*, records m. p. 119—120°). A suspension of this compound (6·78 g.) in a solution of potassium hydrogen sulphide, prepared by saturating a solution of potassium hydroxide (7·9 g.) in water (10 c.c.) with hydrogen sulphide, was heated on the steam-bath for 10 min., the character of the solid undergoing considerable change. Addition of water (200 c.c.) gave a clear solution and acidification with acetic acid afforded *tetrahydro-2-phenyl-4 : 6-dithiono-1 : 3 : 5-triazine* as a yellow solid (5·3 g.), m. p. 246—248°. It crystallised from

ethanol in yellow needles, m. p. 248—249° (Found: C, 49·3; H, 3·5; N, 18·9. $C_9H_7N_3S_2$ requires C, 48·9; H, 3·2; N, 19·0%). Methylation in the usual manner gave **2 : 4-*dimethylthio*-6-*phenyl*-1 : 3 : 5-*triazine*** as colourless needles (from ethanol), m. p. 94—95° (Found: N, 16·9. $C_{11}H_{11}N_3S_2$ requires N, 16·9%).

(*b*) A solution of dithiobiuret (2·7 g.) in ethyl acetate (100 c.c.) was heated under reflux for 2 hr. with benzoyl chloride (2·4 c.c.). Ethyl acetate was then removed *in vacuo*, pyridine (5 c.c.) was added, and heating was continued for 2 hr. on the steam-bath. Addition of aqueous acetic acid gave a brown solid which was purified by solution in aqueous sodium hydroxide, filtration, and reprecipitation with acetic acid. Crystallisation from ethanol afforded yellow needles (1·2 g.), m. p. 245—247° undepressed by the previously described compound.

(*c*) The following methods were unsuccessful: (i) Fusion of benzamidine with perthiocyanic acid at 100° gave an almost quantitative yield of ***benzamidinium thiocyanate***, crystallising from *iso*propanol–ether in needles, m. p. 105—106° (Found: N, 23·2. $C_8H_9N_3S$ requires N, 23·5%), identical with the product obtained by evaporating a methanolic solution of benzamidine and ammonium thiocyanate. (ii) Equimolecular proportions of dithiobiuret and trimethyl orthobenzoate, suspended in ethanol and saturated with dry hydrogen chloride, afforded a solid hydrochloride. Liberation of the base and crystallisation from ethanol gave **2-*methyl*-2-iso*dithiobiuret***, m. p. 134—135° (Found: N, 28·0. $C_3H_7N_3S_2$ requires N, 28·2%). This was identical with the compound obtained by condensation of equimolecular quantities of dithiobiuret and methyl sulphate at 100°, basification of the product, and crystallisation of the free base. In the same way dithiobiuret and ethyl orthoformate yielded **2-*ethyl*-2-iso*dithiobiuret***, m. p. 94—96° (Found: C, 29·4; H, 5·6; N, 25·7. $C_4H_9N_3S_2$ requires C, 29·4; H, 5·5; N, 25·8%), as did dithiobiuret and diethyl sulphate at 100°.

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Nucleotides. Part XXX. Mononucleotides derived from Deoxyadenosine and Deoxyguanosine.*

By D. H. Hayes, A. M. Michelson, and Sir Alexander R. Todd.

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The 3′ and the 5′ phosphates of deoxyadenosine and deoxyguanosine have been synthesised by unambiguous routes. Deoxyadenosine-5′ phosphate and deoxyguanosine-5′ phosphate correspond in their properties to the deoxyadenylic and deoxyguanylic acid previously obtained by enzymic degradation of natural deoxyribonucleic acids.

In previous papers of this series syntheses of the mononucleotides derived from the natural pyrimidine deoxyribonucleosides thymidine and deoxycytidine have been reported. Thymidine-3′ and -5′ phosphate (Part XX; Michelson and Todd, *J.*, 1953, 951) and deoxycytidine-3′ and -5′ phosphate (Part XXIII; Michelson and Todd, *J.*, 1954, 34) were prepared by phosphorylation of suitably protected nucleosides, and the 5′-phosphates were found to be identical respectively with the thymidylic and deoxycytidylic acids obtained by enzymic hydrolysis of natural deoxyribonucleic acids. As an extension of these studies we have now synthesised the 3′- and the 5′-phosphate of the natural purine deoxyribonucleosides deoxyadenosine and deoxyguanosine. The methods adopted (*viz.*, phosphorylation of suitably acylated nucleosides of known structure) were essentially similar to those used for the pyrimidine deoxyribonucleotides but the problem was complicated by the extreme lability of the purine deoxyribonucleosides and their derivatives to acid, and, in the case of deoxyguanosine, by low reactivity of the nucleoside towards acylating agents; these difficulties necessitated certain modifications in the synthetic procedures.

Andersen, Hayes, Michelson, and Todd (*J.*, 1954, 1882) in the course of determining the configuration at the glycosidic centre in deoxyadenosine prepared 3′- and 5′-acetyldeoxy-

* Part XXIX, *J.*, 1954, 2843.

adenosine. These acetyl derivatives, the starting materials for the preparation of the deoxyadenosine phosphates, were found to be more easily prepared by partial deacetylation of 3′ : 5′-diacetyladenosine. Treatment of 3′-acetyldeoxyadenosine with dibenzyl phosphorochloridate in pyridine gave 3′-acetyldeoxyadenosine-5′ dibenzyl phosphate in good yield. After model experiments on the effect of ammonia on 2′ : 3′-*iso*propylideneadenosine-5′ dibenzyl phosphate and on deoxyadenosine, it was found that treatment of 3′-acetyldeoxyadenosine-5′ dibenzyl phosphate with methanolic ammonia under suitable conditions yielded deoxyadenosine-5′ benzyl phosphate in satisfactory yield. Removal of the benzyl group from this compound was effected by hydrogenolysis in aqueous solution buffered to pH 7 with sodium acetate; maintenance of neutral or alkaline pH during hydrogenolysis is essential to avoid fission of the glycosidic linkage. The deoxyadenosine-5′ phosphate so obtained was purified by ion-exchange chromatography and isolated as its calcium salt.

Phosphorylation of 5′-acetyldeoxyadenosine with dibenzyl phosphorochloridate was most unsatisfactory. True, on working up the product and removing protecting groups in the usual way deoxyadenosine-3′ phosphate was obtained but the amount (10 mg. from 2 g. of acetylnucleoside) was so low as to make the process virtually useless. Recourse was had to *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride, a powerful reagent for the preparation of phosphites (Corby, Kenner, and Todd, *J.*, 1952, 3669). This mixed anhydride reacted readily with 5′-acetyldeoxyadenosine in methyl cyanide in presence of 2 : 6-lutidine, giving a reasonable yield (55%) of 5′-acetyldeoxyadenosine-3′ benzyl phosphite. The phosphite was chlorinated with *N*-chlorosuccinimide in chloroform (methyl cyanide could not be used as a vehicle for the reaction), and the crude phosphorochloridate hydrolysed directly with aqueous pyridine, yielding impure 5′-acetyldeoxyadenosine-3′ benzyl phosphate as a brownish gum. Without further purification this product was deacetylated and hydrogenolysed in the manner described for the corresponding 5′-phosphate. Deoxyadenosine-3′ phosphate was formed and, after purification by ion-exchange chromatography, it was isolated as its calcium salt.

The two deoxyadenosine phosphates are readily distinguishable by paper and ion-exchange chromatography. The infra-red spectra of the calcium salts differ from one another but the differences (mainly in the region 8—10 μ) are rather small and the spectra are thus not very useful for characterisation. Their ultra-violet absorption spectra are very similar although a small difference was observed in that a slight inflection at 259 mμ in the spectrum of calcium deoxyadenosine-5′ phosphate was not observed in that of the 3′-phosphate; a similar small difference was observed in the spectra of the two monoacetyl derivatives of deoxyadenosine. Natural deoxyadenylic acid was conclusively identified with deoxyadenosine-5′ phosphate: they were indistinguishable in paper chromatographic and ion-exchange behaviour and in absorption spectrum. Mixtures of the two could not be separated on ion-exchange columns, whereas mixtures of the two synthetic nucleotides and of natural deoxyadenylic acid and deoxyadenosine-3′ phosphate each gave two distinct peaks. Natural deoxyadenylic acid, synthetic deoxyadenosine-5′ phosphate, and deoxyadenosine-5′ benzyl phosphate were all smoothly dephosphorylated by rattlesnake venom (*Crotalus atrox*) whereas deoxyadenosine-3′ phosphate and its benzyl ester were quite unaffected. The deoxyadenosine phosphates and their benzyl esters were unaffected by either ribonuclease or deoxyribonuclease.

For the synthesis of the isomeric deoxyguanosine phosphates it was necessary first to prepare 3′- and 5′-acetyldeoxyguanosine. As in the case of the acetyldeoxyadenosines, mixtures of these compounds were most readily prepared by the partial acetylation of deoxyguanosine or by partial deacetylation of 3′ : 5′-diacetyldeoxyguanosine; the latter procedure had the advantage that it gave much better yields of the 3′-acetyl derivative than the former, which yielded mainly the 5′-isomer. The isomeric acetyl derivatives were separated by countercurrent distribution but their orientation was more difficult than that of the monoacetyldeoxyadenosines, since no reference substance corresponding to 3′-acetyl-5′-trityldeoxyadenosine was available and a less direct method was employed. An investigation of the acid hydrolysis of the acetylated purine deoxyribonucleosides, in which the glycosidic linkage is extremely labile, showed that the acetates of 2-deoxy-D-

ribose were not decomposed under conditions which hydrolysed the glycosidic link completely. It was also possible to differentiate 3- and 5-acetyl-2-deoxy-D-ribose clearly by paper chromatography in several solvent systems; the differences in R_F values were small but adequate. Hydrolyses were therefore carried out side by side on the monoacetyl derivatives of deoxyadenosine and deoxyguanosine, and the two latter were oriented by the correspondence of the products with those from the deoxyadenosine derivatives whose orientation was already known. Neither of the monoacetyldeoxyguanosines has a proper melting point but they behave rather differently when heated, since 5′-acetyldeoxyguanosine crystallises from aqueous ethanol with 1 mol. of water which it loses at 125—130° whereas 3′-acetyldeoxyguanosine crystallises from the same solvent in anhydrous form. The two isomers are most readily distinguished by paper chromatography.

Since, in experiments directed to other ends, we had failed to bring about reaction between the monoacetyl derivatives of deoxyguanosine and toluene-*p*-sulphonyl chloride or methanesulphonyl chloride no attempt was made to phosphorylate them with dibenzyl phosphorochloridate. Instead they were phosphorylated by using *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride, and the acetyldeoxyguanosine benzyl phosphites, which were produced in *ca.* 30% yield, were converted into the deoxyguanosine nucleotides as described above for deoxyadenosine-3′ phosphate. Deoxyguanosine-3′ and -5′ phosphate, which can be distinguished by paper chromatography, were isolated as their barium salts. No specimen of pure natural deoxyguanylic acid was available; there is, however, no doubt that the natural acid is identical with deoxyguanosine-5′ phosphate since the latter and its benzyl ester, like the natural product, were readily dephosphorylated by rattlesnake venom whereas the 3′-phosphate was unaffected. Like the corresponding deoxyadenosine derivatives, neither the deoxyguanosine phosphates nor deoxyguanosine-5′ benzyl phosphate were affected by ribonuclease or deoxyribonuclease.

Experimental

3′ : 5′-Diacetyldeoxyadenosine.—Acetic anhydride (10 c.c.) was added to a solution of anhydrous deoxyadenosine (4 g.) in pyridine (20 c.c.), and the mixture left overnight at room temperature, then cooled to 0° and poured into ice–water (200 c.c.) with vigorous stirring. The aqueous solution was extracted twice with chloroform, and the combined extracts were washed with cold dilute sodium hydrogen carbonate solution, then with water, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue of *3′ : 5′-diacetyldeoxyadenosine* crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 151—152° (4·6 g.) (Found, in material dried for 15 hr. at 120°/10^{-3} mm.: C, 50·4; H, 5·2; N, 20·9. $C_{14}H_{17}O_5N_5$ requires C, 50·2; H, 5·1; N, 20·9%).

3′-Acetyldeoxyadenosine and 5′-Acetyldeoxyadenosine.—Saturated methanolic ammonia (75 c.c.) was added to a solution of 3′ : 5′-diacetyldeoxyadenosine (2·5 g.) in ethanol (250 c.c.), and the mixture left at room temperature for 1½ hr. Solvent was then removed under reduced pressure and the residue separated into its components by countercurrent distribution, using an ethyl acetate–water system as previously described (Anderson, Hayes, Michelson, and Todd, *loc. cit.*), to give deoxyadenosine (0·38 g.), 5′-acetyldeoxyadenosine (0·64 g.), 3′-acetyldeoxyadenosine (0·33 g.), and unchanged 3′ : 5′-diacetyldeoxyadenosine (0·82 g.).

3′-Acetyldeoxyadenosine-5′ Dibenzyl Phosphate.—A solution of 3′-acetyldeoxyadenosine (2 g., 1 mol.; dried for 24 hr. at 100°/0·5 mm.) in anhydrous pyridine (150 c.c.) was cooled to its f. p. (acetone–carbon dioxide). Dibenzyl phosphorochloridate (from 7·2 g., 4 mols., of dibenzyl phosphite) was added and the mixture kept at, or just above, its m. p. for 4 hr., then at room temperature overnight.

Aqueous sodium carbonate (6 g. in 40 c.c. of water) was added and the mixture filtered. The filtrate was evaporated to dryness under reduced pressure (temp. $\gg$ 35°) and the residue evaporated several times with ethanol (25 c.c.), after which it was dissolved in chloroform (25 c.c.). The chloroform solution was washed successively with saturated sodium hydrogen carbonate solution (3 × 50 c.c.) and water (2 × 50 c.c.) and evaporated at 0·01 mm. The residue (4·2 g.) was dissolved in dry acetone (10 c.c.); ether (20 c.c.) followed by light petroleum (70 c.c.; b. p. 60—80°) was added, and the mixture was set aside overnight. The supernatant liquid was decanted and solvent removed from the residue at room temp./0·01 mm. The brownish gum (3·0 g.) so obtained was redissolved in chloroform, the solution washed with sodium hydrogen carbonate and water and evaporated under reduced pressure, and the residue treated as before

with acetone, ether, and light petroleum. The precipitated resin was washed with light petroleum and converted into an amber-coloured solid foam (2·4 g., 63%) by evacuation to 0·01 mm. Paper chromatography in *n*-butanol–water (86 : 14) showed that this product was essentially a single substance (R_F 0·83) contaminated with small amounts of other slower-running substances. The crude 3′-acetyldeoxyadenosine-5′ dibenzyl phosphate was further purified by refluxing it with dry ether (1 c.c. of ether for 10 mg.) for 2 hr., decanting the supernatant liquid, and leaving the residue at 10^{-4} mm. It still contained some impurities (Found : C, 57·1; H, 5·3; N, 12·7%. Calc. for $C_{26}H_{28}O_7N_5P$: C, 56·4; H, 5·1; N, 10·6%).

Deoxyadenosine-5′ Benzyl Phosphate.—The above crude 3′-acetyldeoxyadenosine-5′ dibenzyl phosphate (2·3 g.) was dissolved in saturated methanolic ammonia (50 c.c.), and the solution left at room temperature for 100 hr. before evaporation to dryness at room temp./0·1 mm. The solid foam (2·2 g.) contained some unhydrolysed dibenzyl ester (paper chromatography); it was therefore dissolved in water (100 c.c.), and the solution washed with ethyl acetate (5 × 100 c.c.), the aqueous solution and the ethyl acetate washings being evaporated separately. The ethyl acetate washings on evaporation gave a gum (0·5 g.) which was, on the basis of its paper chromatographic behaviour, probably in the main deoxyadenosine-5′ dibenzyl phosphate; treatment of this residue with methanolic ammonia (10 c.c.) as before yielded a further amount of material identical with the product obtained by evaporating the aqueous solution; the combined yield was 1·53 g. There is no doubt that this product was essentially a single nucleotide but it behaved on paper chromatography like a salt. In the *n*-butanol–water (86 : 14) system it gave two spots (R_F 0·15 and 0·41). When these spots were eluted and the eluates run separately on fresh chromatograms, with the same system, it was found that (*a*) the material of R_F 0·15 gave only one spot (R_F 0·15) and (*b*) the material of R_F 0·41 gave two spots (R_F 0·15 and 0·41). This behaviour is presumably due to dissociation of a salt. In acidic or basic solvent systems only one spot is observed and in these systems the original product as well as both the materials into which it was resolved by chromatography in *n*-butanol–water gave the same single spot at the same R_F.

A solution of the product (150 mg.) in water (0·5 c.c.) was applied as a band on a strip of Whatman No. 3 paper (19 × 36 cm.), and the chromatogram developed with *n*-butanol–water (86 : 14); it showed two bands (by ultra-violet absorption) of R_F 0·1—0·14 and 0·34—0·4. The latter band was cut out and eluted with water, and the eluate evaporated. The pale brownish glass (85 mg.) appeared to be mainly deoxyadenosine-5′ benzyl benzylammonium phosphate (Found : C, 52·2; H, 6·3; N, 14·7; P, 5·4%; ratio N : P, 2·72. Calc. for $C_{24}H_{29}O_6N_6P$: C, 54·5; H, 5·5; N, 15·9; P, 5·9%; ratio N : P, 2·71).

For further stages in synthesis the crude product obtained directly from the washed aqueous solution of the ammonia-treated starting material was used directly since it was presumably a mixture of the ammonium and the benzylammonium salt of the desired phosphate.

Deoxyadenosine-5′ Phosphate.—The above monobenzyl ester (1·27 g.) was dissolved in distilled water (50 c.c.). Sodium acetate ("AnalaR;" 1·2 g.) and 10% palladised charcoal (100 mg.) were added and the mixture was shaken with hydrogen at room temperature/1 atm. for 20 hr., fresh catalyst (100 mg.) being added after 2 and 14 hr. The filtered solution was brought to pH 10 with ammonia and applied to a column of anion-exchange resin (Dowex 2, chloride form, 400 mesh; 6 cm. × 7 sq. cm.). The column was washed successively with aqueous 0·01M-ammonium chloride (500 c.c.) and hydrochloric acid (500 c.c. of 0·001N, followed by 7 l. of 0·003N). The eluate was collected in fractions of 10 c.c., the optical density of each at 260 mμ being determined. The desired product was located in the 0·003N-acid eluates; the bulked eluates containing it (4400 c.c.) were neutralised (pH 7·5) with carbonate-free lime water, and the solution was evaporated to small bulk (200 c.c.) under reduced pressure at $\Rightarrow 35°$. Ethanol (600 c.c.) was added, the mixture left overnight, and the precipitated calcium salt (0·95 g.) collected by centrifugation. The precipitate was warmed to 40° with distilled water and filtered through Hyflo Supercel, and the filtrate diluted with ethanol (900 c.c.) and set aside at 0° overnight. Calcium deoxyadenosine-5′ phosphate (700 mg.) separated and was collected by centrifugation.

Final purification was effected by reprecipitation from aqueous solution with ethanol, and the white amorphous salt dried at 120°/1 mm. during 24 hr.; its analyses presumed a *dihydrate* (Found : C, 29·6; H, 3·7; P, 7·9. $C_{10}H_{12}O_6N_5PCa,2H_2O$ requires C, 29·6; H, 4·0; P, 7·7%). The salt had $[\alpha]_D^{19}$ −26° (*c*, 0·38 in H_2O); Klein and Thannhauser (*Z. physiol. Chem.*, 1934, **224**, 252) record $[\alpha]_D^{19}$ −38° (*c*, 0·23 in H_2O) for natural deoxyadenylic acid. Light absorption : In N/100-HCl, max. at 257·5 mμ (ε 13,580), min. at 227·5 mμ (ε 2710), optical density ratios 250/260 = 0·84 and 280/260 = 0·23. In H_2O, max. at 260 mμ (ε 13,600), min. at 227 mμ

(ε 1850), optical density ratios 250/260 = 0·78 and 280/260 = 0·16. In N/100-NaOH, max. at 260 mμ (ε 14,140), min. at 227·5 mμ (ε 2554), optical density ratios 250/260 = 0·79 and 280/260 = 0·18.

The synthetic nucleotide was directly compared with natural deoxyadenylic acid and was identical with it in ultra-violet and infra-red spectrum, and in paper chromatographic and ion-exchange characteristics (see below). Like the natural nucleotide it was completely converted into deoxyadenosine and inorganic phosphate by rattlesnake venom in 3 hr. at 37°.

5′-Acetyldeoxyadenosine-3′ Benzyl Phosphite.—5-Acetyldeoxyadenosine (1 g., 1 mol.; dried for 24 hr. at 60°/1 mm.) and anhydrous 2 : 6-lutidine (0·73 g., 2 mols.) were dissolved in anhydrous methyl cyanide (150 c.c.). *O*-Benzylphosphorous *OO*-diphenylphosphoric anhydride (2·75 g., 2 mols.) (Corby, Kenner, and Todd, *loc. cit.*) was added and the mixture left overnight at room temperature. Solvents were removed at room temperature under reduced pressure and the residue was dissolved in chloroform (75 c.c.). The chloroform solution was washed successively with water (4 × 20 c.c.), saturated aqueous sodium hydrogen carbonate (5 × 20 c.c.), and water (5 × 20 c.c.), dried, and evaporated, and the residue was twice evaporated with ethanol, giving an almost colourless resin (1·37 g.). Paper chromatography in *n*-butanol–water (86 : 14) showed that this resin contained two substances, one the desired phosphite (R_P 0·64) and the other (R_P 0·9) probably dibenzyl phosphite (cf. Corby, Kenner, and Todd, *loc. cit.*). The product was freed from the faster-moving component by dissolution in chloroform (5 c.c.), pouring the solution into *cyclo*hexane (200 c.c.), and setting the whole aside overnight. The supernatant liquid was decanted and the residual *5′-acetyldeoxyadenosine-3′ benzyl phosphite* (0·83 g., 55%) converted into a yellowish solid foam by evacuation to 0·1 mm. (Found : C, 50·1; H, 5·0; N, 16·1; P, 6·5%; ratio N : P, 2·46. $C_{19}H_{21}O_6N_5P,0{\cdot}5H_2O$ requires C, 50·1; H, 4·9; N, 15·4; P, 6·8%; ratio N : P, 2·26). The same product was obtained in 40% yield when dimethylformamide was used in place of methyl cyanide in the above preparation.

Deoxyadenosine-3′ Phosphate.—5′-Acetyldeoxyadenosine-3′ benzyl phosphite (0·5 g., 1 mol.) was dissolved in " AnalaR " chloroform (20 c.c.), and *N*-chlorosuccinimide (0·165 g., 1·1 mols.) was added. The mixture was left for 5 hr. at room temperature, then aqueous pyridine (20 c.c.; pyridine : water = 8 : 1) was added, and the whole shaken for 12 hr. Solvents were removed under reduced pressure at room temperature and the residue was twice evaporated with ethanol, giving crude 5′-acetyldeoxyadenosine-3′ benzyl phosphate as a brownish gum (0·9 g.).

This product was dissolved in half-saturated methanolic ammonia (40 c.c.) and after 12 hr. at room temperature the solution was evaporated at ⩾40°, the residue dissolved in distilled water (20 c.c.), and crystalline sodium acetate (0·7 g.; " AnalaR ") added. The solution was then hydrogenated at room temperature and pressure by use of 10% palladised charcoal (100 mg.) during 20 hr., fresh catalyst being added twice during the operation. The solution was filtered, brought to pH 10 with ammonia, and applied to a column of anion-exchange resin (Dowex-2, chloride form, 400 mesh; 5 cm. × 2·2 sq. cm.). Elution was carried out successively with aqueous ammonium chloride (3700 c.c.; 0·01M) and hydrochloric acid (950 c.c. of 0·001N, followed by 2200 c.c. of 0·003N). The eluate was collected in 10-c.c. fractions, their optical density at 260 mμ being determined as usual. The desired phosphate collected in fractions 435—490 which were bulked, brought to pH 7·5 with carbonate-free lime water, and evaporated under reduced pressure at ⩾45° to 30 c.c. The solution was filtered and *calcium deoxyadenosine-3′ phosphate* (88 mg.) precipitated as a white amorphous solid by ethanol (90 c.c.). For further purification the salt was twice reprecipitated by dissolving it in water (10 c.c.) and adding ethanol (30 c.c.); thus obtained it appeared to be hydrated (Found, in material dried for 24 hr. at 100°/1 mm. : C, 28·4; H, 4·2; N, 15·2; P, 6·8%; ratio N : P, 2·24. $C_{10}H_{13}O_6N_5PCa,3H_2O$ requires C, 28·3; H, 4·3; N, 16·5; P, 7·3%; ratio N : P, 2·26). The substance had $[\alpha]_D^{19}$ −10·8° (*c*, 0·46 in H_2O). Light absorption : In N/100-HCl, max. at 257—258 mμ (ε 14,650), min. at 229 mμ (ε 3390), optical density ratios 250/260 = 0·83 and 280/260 = 0·23. In H_2O, max. at 259—260 mμ (ε 14,450), min. at 226 mμ (ε 1915), optical density ratios 250/260 = 0·77 and 280/260 = 0·16. In N/100-NaOH, max. at 259—260 mμ (ε 15,090), min. at 227 mμ (ε 2050), optical density ratios 250/260 = 0·76 and 280/260 = 0·16. The synthetic nucleotide was recovered unchanged after incubation with rattlesnake venom at 37°.

Paper Chromatography of Deoxyadenosine Phosphates.—Ascending chromatograms, Whatman No. 1 paper. Solvent systems : I, *n*-butanol–water (86 : 14); II, *n*-butanol–acetic acid–water (4 : 1 : 5); III, *tert.*-butanol–acetic acid–water (5 : 4 : 1); IV, 5% aqueous disodium hydrogen phosphate–*iso*pentyl alcohol (3 : 2); V, ethanol–ammonia–water (80 : 4 : 16); VI, *iso*propanol–ammonia–water (7 : 1 : 2). Spots were detected on the chromatograms by (*a*) ultra-violet absorption, (*b*) cysteine hydrochloride spray for 2-deoxyribose derivatives (Stumpf, *J. Biol.*

Chem., 1947, **169**, 367), and (*c*) perchloric acid–ammonium molybdate spray for phosphorus (Hanes and Isherwood, *Nature*, 1949, **174**, 1107). The R_F obtained are tabulated.

System :	I	II	III	IV	V	VI
Deoxyadenosine-3′ phosphate	0	0·10	—	0·64	—	0·08
Deoxyadenosine-5′ phosphate	0	0·10	0·12	0·70	0	0·08
Natural deoxyadenylic acid	0	0·10	—	0·70	—	0·08
Deoxyadenosine-3′ benzyl phosphate	0·14	0·44—46	0·46	0·55	0·37—44	0·54
Deoxyadenosine-5′ benzyl phosphate	0·15	0·40	0·46	0·64	0·40—44	0·52

Ion-exchange Chromatography of Deoxyadenosine Phosphates.—The samples of calcium salts (1—1·5 mg.) were dissolved in 0·0075N-ammonia (0·5 c.c.) and absorbed on a column (7 cm. × 1 cm. diam.) of Dowex-2 resin (400 mesh) in the chloride form. Elution was carried out with 0·03M-formic acid, eluates being collected in 10-c.c. fractions with a flow rate of 0·6—1 c.c./min., and optical density at 260 mμ was determined on each fraction. Number of fractions to peak : Deoxyadenosine-3′ phosphate, 95; deoxyadenosine-5′ phosphate, 56; natural deoxyadenylic acid, 56. The last two materials were indistinguishable and could not be separated on the column when mixed.

3′ : 5′-Diacetyldeoxyguanosine.—Acetic anhydride (10 c.c.) was added to a solution of anhydrous deoxyguanosine (4 g.; dried for 12 hr. at 100/1 mm.) in dimethylformamide (50 c.c.) and pyridine (20 c.c.), and the mixture left overnight at room temperature, then cooled to 0° and poured into ice–water (350 c.c.) with vigorous stirring. After 1 hr. the crystalline precipitate of *3′ : 5′-diacetyldeoxyguanosine* (4·14 g.) was collected, washed with water, and dried. Recrystallised from 90% ethanol it forms colourless needles, m. p. 222° (decomp.) (Found, in material dried for 15 hr. at 120°/10^{-3} mm. : C, 48·1; H, 5·0; N, 20·1. $C_{14}H_{17}O_6N_5$ requires C, 47·9; H, 4·8; N, 19·9%). The substance had R_F 0·49 when run on paper with *n*-butanol–water (86 : 14) as solvent system, and $[\alpha]_D^{18}$ −38° [*c*, 0·3192 in ethanol–water (1 : 9)].

3′-Acetyldeoxyguanosine and 5′-Acetyldeoxyguanosine by Partial Hydrolysis of 3′ : 5′-Diacetyldeoxyguanosine.—The above diacetyl derivative (3·2 g.) was dissolved in aqueous ethanol (600 c.c., containing 12% of water by vol.) and saturated methanolic ammonia (150 c.c.) was added. After 3½ hr. at room temperature the mixture was evaporated to dryness under reduced pressure, first at room temperature until the ammonia had been removed and then at ≯35°. The product was separated into its components by countercurrent distribution in an automatically operated 100-stage apparatus. The separation was similar to that described for the acetyldeoxyadenosines (Anderson, Hayes, Michelson, and Todd, *loc. cit.*), but the solvent system (empirically selected) was ethyl acetate–*n*-butanol–water (100 : 25 : 125 by vol.), and the process was continued until 165 withdrawal stages had been completed. Determination of the optical density at 255 mμ of suitably spaced fractions gave a distribution curve showing three distinct peaks. Fractions corresponding to each of these peaks were separately bulked, as were the withdrawal stages as follows.

Fractions 0—32. Evaporation and recrystallisation of the residue gave deoxyguanosine (0·5 g.).

Fractions 33—56. Evaporation followed by recrystallisation from 40% ethanol gave *5′-acetyldeoxyguanosine* (0·8 g.) as large clusters of colourless hydrated needles. It frothed at 125—130°, then set to a colourless glass which slowly became opaque above 170° and charred on further heating (Found, in material dried at room temperature : C, 44·5; H, 5·2; N, 21·5. $C_{12}H_{15}O_5N_5,H_2O$ requires C, 44·0; H, 5·2; N, 21·4. Found, in material dried for 24 hr. at 120°/0·1 mm. : C, 46·6; H, 5·1; N, 22·5. $C_{12}H_{15}O_5N_5$ requires C, 46·6; H, 4·9; N, 22·7%). On paper chromatography in *n*-butanol–water (86 : 14) it had R_F 0·32. It had $[\alpha]_D^{18·5}$ −33° [*c*, 0·4212 in ethanol–water (1 : 9)].

Fractions 62—98. The residue left on evaporation was recrystallised from 90% ethanol, giving *3′-acetyldeoxyguanosine* (0·45 g.) as colourless plates which charred without melting above 240° (Found, in material dried for 12 hr. at 100°/0·5 mm.: C, 46·5; H, 5·2; N, 22·5%), R_F 0·38 in *n*-butanol–water (86 : 14), $[\alpha]_D^{19·5}$ −12·5° [*c*, 0·3448 in ethanol–water (1 : 9)].

Withdrawal stages 0—165. From the combined withdrawal stages 3′ : 5′-diacetyldeoxyguanosine (0·85 g.), m. p. and mixed m. p. 221—222°, was obtained by evaporation and recrystallisation.

3′-Acetyldeoxyguanosine and 5′-Acetyldeoxyguanosine by Partial Acetylation of Deoxyguanosine.—Deoxyguanosine (10 g.; dried for 24 hr. at 100°/1 mm.) was dissolved in dry dimethylformamide (1 l.), and a solution of freshly redistilled acetic anhydride (41·8 c.c., 12 mols.) in anhydrous pyridine (300 c.c.) added. The mixture was left for 9 hr. at room temperature, then water (300 c.c.) was added, and the resulting solution was evaporated to dryness under reduced

pressure at +60°. The residue (12·1 g.) was twice evaporated with water (100 c.c.), and the product then separated into its components by countercurrent distribution as described in the previous experiment. The yields obtained were: deoxyguanosine, 1 g.; 5′-acetyldeoxyguanosine 5·5 g.; 3′-acetyldeoxyguanosine, 0·57 g.; 3′ : 5′-diacetyldeoxyguanosine, 3 g.

Orientation of the Monoacetyldeoxyguanosines.—The acid hydrolysis of the unsubstituted nucleosides as well as of the two monoacetyldeoxyguanosines and of 3′-acetyldeoxyadenosine and 5′-acetyldeoxyadenosine was studied first under varying conditions, and the following procedure was finally adopted. The nucleosides and their acetyl derivatives (5 mg.) were treated with 0·02N-hydrochloric acid (2·5 c.c.). All the compounds dissolved completely in the cold, without decomposition, in 10—15 min. The solutions were then heated at 100°, the degree of hydrolysis and the nature of the products being examined by paper chromatography at intervals. Chromatograms with appropriate controls were run in various solvent systems, and the hydrolysis products were detected on chromatograms by ultra-violet absorption (purine derivatives) and by the cysteine hydrochloride (Stumpf, *loc. cit.*) and aniline phthalate (Partridge, *Nature*, 1949, **174**, 443) sprays (for 2-deoxy-D-ribose derivatives). The results may be summarised as follows: (1) The nucleosides are completely hydrolysed to purine and sugar after 2—5 min. at 100°. (2) The glycosidic linkage in the monoacetylnucleosides is completely hydrolysed after 5 min. at 100° (10 min. required for the 3′ : 5′-diacetyl derivatives). (3) The monoacetyl derivatives of 2-deoxy-D-ribose produced from the monoacetylnucleosides begin to lose acetyl groups only after 10 min. at 100°. (4) The isomeric 3′- and 5′-acetyl-2-deoxy-D-ribose can be distinguished chromatographically in three solvent systems.

The monoacetyl derivatives of deoxyadenosine and deoxyguanosine (5 mg.) were therefore separately heated at 100° for 5 min. with 0·02N-hydrochloric acid (2·5 c.c.), and the hydrolysis products were run (ascending chromatograms, Whatman No. 1 paper) in the following solvent systems: I, *n*-butanol–water (86 : 14); II, pyridine–ethyl acetate–water (1 : 2 : 2); III, *n*-butanol–acetic acid–water (4 : 1 : 5); IV, *n*-butanol–pyridine (Chargaff *et al.*, *J. Biol. Chem.*, 1949, **177**, 405). The results are tabulated, the abbreviations used being U.V. = ultra-violet spot, D = cysteine spot, AP = aniline phthalate spot.

Substance hydrolysed	R_F with staged solvent system and method of detection											
	I			II			III			IV		
	UV	D	AP	UV	D	AP	UV	D	AP	UV	D	AP
Acetyldeoxyadenosine:												
3′-	0·40	0·58	0·60	0·75	0·93	0·93	0·50	0·69	0·68	0·57	0·79	0·82
5′-	0·40	0·63	0·64	0·75	0·94	0·93	0·50	0·72	0·70	0·57	0·82	0·84
Acetyldeoxyguanosine:												
3′-	0·16	0·59	0·60	0·59	0·92	0·89	0·32	0·69	0·67	0·39	0·79	0·82
5′-	0·16	0·63	0·64	0·59	0·93	0·90	0·32	0·72	0·69	0·40	0·83	0·85

Small differences in the R_F found for the same product in the same solvent system when detected by different reagents are due to the fact that each vertical column in the Table summarises the results from a separate paper strip.

5′-Acetyldeoxyguanosine-3′ Benzyl Phosphite.—5′-Acetyldeoxyguanosine (1·98 g., 1 mol.; dried for 12 hr. at 120°/1 mm.) was suspended in anhydrous methyl cyanide (200 c.c.). Dry 2 : 6-lutidine (1·38 g., 2 mols.) and *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (5·2 g., 2 mols.) were added and the suspension was shaken at room temperature for 50 hr. Chromatographic study of the solution showed that the major product was the desired phosphite but that a considerable amount of unchanged starting material was also present. After removal of methyl cyanide at room temperature the residue was dissolved in chloroform, and the solution washed successively with saturated aqueous sodium hydrogen carbonate (5 × 20 c.c.) and water (5 × 20 c.c.) and then evaporated to dryness at room temperature. The gummy residue (2·2 g.) was dissolved in chloroform (5 c.c.), and the solution poured into dry *cyclo*hexane (200 c.c.). The white amorphous precipitate of *5′-acetyldeoxyguanosine-3′ benzyl phosphite* (0·85 g., 28%) was collected and dried *in vacuo* at room temperature. Chromatography in *n*-butanol–water (86 : 14) showed that the product contained traces of two phosphorus-free substances (probably guanine and 5′-acetyldeoxyguanosine) (Found, in material dried for 48 hr. at 60°/2 mm.: C, 49·2; H, 5·8; N, 14·4; P, 6·3%; ratio N : P, 2·29. $C_{19}H_{22}O_7N_5P$ requires C, 49·3; H, 4·7; N, 15·1; P, 6·7%; ratio N : P, 2·26). The acetonitrile used as vehicle in this preparation could be replaced with dimethylformamide (in which the starting material is more soluble) without material alteration in the yield.

Deoxyguanosine-3′ Phosphate.—The above phosphite (0·5 g., 1 mol.) was treated in chloroform

(20 c.c.) containing 2% ethanol by volume with *N*-chlorosuccinimide (167 mg., 1·1 mols.). The mixture was shaken and set aside at room temperature. After 1 hr. a white solid began to separate and after 5 hr. aqueous pyridine (20 c.c. containing 10% water by vol.) was added and the mixture set aside overnight. Solvents were removed under reduced pressure and the residue was twice evaporated with ethanol (20 c.c.), giving crude 5′-acetyldeoxyguanosine-3′ benzyl phosphate as a yellow resin (0·9 g.).

This resin was now dissolved in half-saturated methanolic ammonia (40 c.c.), and the solution left overnight at room temperature. It was then evaporated and the residue taken up in distilled water (20 c.c.) and hydrogenated in presence of sodium acetate (0·7 g.) in presence of 10% palladised charcoal (100 mg.). The solution obtained was worked up exactly as described above for the corresponding deoxyadenosine nucleotide, purification being effected by anion-exchange chromatography. The nucleotide was concentrated in fractions 456—654 (*i.e.*, 0·003N-hydrochloric acid eluate). These fractions were combined, brought to pH 7·5 with carbonate-free aqueous barium hydroxide, concentrated to small bulk (120 c.c.) *in vacuo* at $> 40°$, and filtered, and *barium deoxyguanosine-3′ phosphate* (120 mg.) was precipitated by ethanol (360 c.c.). The salt, a white amorphous powder, was purified by two further precipitations from water with ethanol (Found, in material dried for 24 hr. at 100°/1 mm.: C, 23·5; H, 3·7; N, 12·9; P, 5·8%; ratio N : P, 2·25. $C_{10}H_{12}O_7N_5PBa,2H_2O$ requires C, 23·2; H, 3·1; N, 13·5; P, 6·0%; ratio N : P, 2·26). The nucleotide was quite unaffected by rattlesnake venom at 37°. Light absorption: In N/100-HCl, max. at 254—256 mμ (ε 11,610), min. at 227—228 mμ (ε 3750), inflection at 274 mμ (ε 8220), optical density ratios 250/260 = 1·01 and 280/260 = 0·72. In water, max. at 252—253 mμ (ε 12,150), min. at 225 mμ (ε 4090), inflection at 265 mμ (ε 9202), optical density ratios 250/260 = 1·15 and 280/260 = 0·72. In N/100-NaOH, max. at 262—265 mμ (ε 11,240), min. at 231 mμ (ε 5380), optical density ratios 250/260 = 0·90 and 280/260 = 0·67. The salt had $[\alpha]_D^{19·5}$ −8·5° (*c*, 0·412 in H_2O).

3′-Acetyldeoxyguanosine-5′ Benzyl Phosphite.—3′-Acetyldeoxyguanosine (1·03 g., 1 mol.; dried for 12 hr. at 120°/1 mm.) was suspended in dry methyl cyanide (100 c.c.). Dry 2 : 6-lutidine (0·71 g., 2 mols.) and *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (2·26 g., 2 mols.) were added. The mixture was shaken at room temperature for 50 hr. and worked up as described for the 3′-isomer (above). *3′-Acetyldeoxyguanosine-5′ benzyl phosphite* (460 mg., 30%) was obtained in slightly impure condition as a white solid by precipitation from chloroform with *cyclo*hexane (Found, in material dried for 60 hr. at 60°/2 mm.: C, 46·1; H, 5·0; N, 14·8; P, 6·6%; ratio N : P, 2·23. $C_{19}H_{22}O_7N_5P$ requires C, 49·3; H, 4·7; N, 15·1; P, 6·7%; ratio N : P, 2·26).

Deoxyguanosine-5′ Phosphate.—The preparation of this substance from 3′-acetyldeoxyguanosine-5′ benzyl phosphite (0·53 g.) was carried out as described above for the 3′-isomer. The nucleotide was isolated as its hydrated *barium salt* (33 mg.) by precipitation from aqueous solution with ethanol (Found, in material dried for 24 hr. at 100°/1 mm.: C, 21·9; H, 3·7; N, 12·1; P, 5·7%; ratio N : P, 2·11. $C_{10}H_{12}O_7N_5PBa,4H_2O$ requires C, 21·7; H, 3·6; N, 12·6; P, 5·6%; ratio N : P, 2·26). The salt had $[\alpha]_D^{19·5}$ −18·6° (*c*, 0·366 in H_2O); Klein and Thannhauser (*Z. physiol. Chem.*, 1933, **218**, 173) reported $[\alpha]_D^{19}$ −31° (*c*, 0·46 in H_2O). Light absorption: In N/100-HCl, max. at 254—256 mμ (ε 13,650), min. at 227 mμ (ε 3970), inflection at 273 mμ (ε 9810), optical density ratios 250/260 = 1·01 and 280/260 = 0·69. In H_2O, max. at 252—255 mμ (ε 15,680), min. at 225 mμ (ε 5170), inflection at 265 mμ (ε 11,270), optical density ratios 250/260 = 1·09 and 280/260 = 0·68. In N/100-NaOH, max. at 263—264 mμ (ε 12,870) min. at 230—231 mμ (ε 5440), optical density ratios 250/260 = 0·88 and 280/260 = 0·66. Like natural deoxyguanylic acid the synthetic product was completely dephosphorylated by rattlesnake venom in 3½ hr. at 37°.

Paper Chromatography of Deoxyguanosine Phosphates.—Ascending chromatograms on Whatman No. 1 paper. Solvent systems: I, *n*-butanol–acetic acid–water (4 : 1 : 5); II, aqueous disodium hydrogen phosphate (5%)–*iso*pentyl alcohol (3 : 2); III, *iso*propanol–ammonia–water (7 : 1 : 2); IV, aqueous potassium dihydrogen phosphate (5%)–*iso*pentyl alcohol (3 : 2).

	I	II	III	IV
Deoxyguanosine-3′ phosphate	0·07	0·76	0·03	0·60
Deoxyguanosine-5′ phosphate	0·07	0·78	0·03	0·65

Our thanks are offered to the Royal Commissioners for the Exhibition of 1851 for an Overseas Scholarship (held by D. H. H.) and to the Rockefeller Foundation and Roche Products Ltd. for grants.

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Deoxyribonucleosides and Related Compounds. Part V. cyclo Thymidines and other Thymidine Derivatives. The Configuration at the Glycosidic Centre in Thymidine.*

By A. M. Michelson and Sir Alexander R. Todd.

[Reprint Order No. 5841.]

A number of halogenodeoxythymidines have been prepared *via* the corresponding methanesulphonyl- or toluene-*p*-sulphonyl-thymidines, and have been converted by reduction into the corresponding deoxythymidines. When heated with silver acetate in methyl cyanide containing traces of base 3′-deoxy-3′- and 5′-deoxy-5′-iodothymidine gave halogen-free compounds formulated as O^2 : 3′-*cyclo*thymidine and O^2 : 5′-*cyclo*thymidine respectively. Similarly, treatment of 3′ : 5′-dimethanesulphonylthymidine with alcoholic ammonia yields 5′-methanesulphonyl O^2 : 3′-*cyclo*thymidine. The behaviour of these *cyclo*thymidines towards acid and alkali has been studied and their formation is in accord with the formulation of thymidine as 3-β-2′-deoxy-D-ribofuranosylthymine; the β-configuration has also been confirmed by *X*-ray crystallographic examination of 5′-bromo-5′-deoxythymidine. Silver dibenzyl phosphate reacts with 3′-acetyl-5′-deoxy-5′-iodothymidine, to give a product from which by removal of protecting groups thymidine-5′ phosphate is obtained.

Although the chemistry of the ribonucleosides and their derivatives has been extensively studied, the deoxyribonucleosides have received scant attention largely because of their relative inaccessibility. Levene and Tipson (*J. Biol. Chem.*, 1935, **109**, 623) treated thymidine (I; R = R′ = OH) with toluene-*p*-sulphonyl chloride and obtained a mixture of a ditoluene-*p*-sulphonylthymidine (presumably 3′ : 5′-) and a chloro-toluene-*p*-sulphonylthymidine (5′-chloro-5′-deoxy-3′-toluene-*p*-sulphonylthymidine ?) but their products were not characterised. They also observed (*loc. cit.*) that 5′-tritylthymidine gave a toluene-*p*-sulphonyl derivative which appeared to be very reactive in that when heated with sodium iodide for 2 hr. at 100°, *i.e.*, the standard conditions of Oldham and Rutherford (*J. Amer. Chem. Soc.*, 1932, **54**, 366), some 30% replacement of the toluene-*p*-sulphonyl group occurred. These preliminary studies formed the starting point for the work described in this paper, since both 3′-deoxy-3′-iodothymidine and 5′-deoxy-5′-iodothymidine were of interest to us as possible intermediates in polynucleotide synthesis using methods of the type described by Elmore and Todd (*J.*, 1952, 3681).

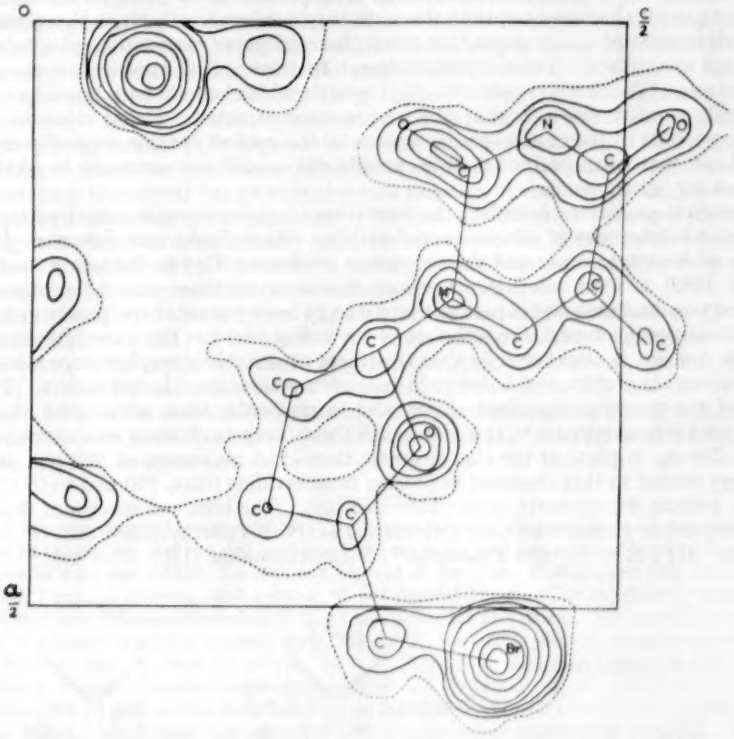
In view of Levene and Tipson's observations (*loc. cit.*) it was decided to use methanesulphonyl derivatives in the first instance, since the methanesulphonyl group is rather less readily replaced than the toluene-*p*-sulphonyl group. Thymidine (I; R = R′ = OH) reacted readily with methanesulphonyl chloride, giving a good yield of 3′ : 5′-dimethanesulphonylthymidine (I; R = R′ = O·SO_2·Me); when heated with sodium iodide the latter gave a rather complex mixture of products containing mainly 5′-deoxy-5′-iodo-3′-methanesulphonylthymidine (I; R = O·SO_2·Me, R′ = I). When heated with lithium bromide at 100° for 2 hours, however, the diester (I; R = R′ = O·SO_2·Me) gave 3′ : 5′-dibromo-3′ : 5′-dideoxythymidine (I; R = R′ = Br). Hydrogenation of this dibromo-compound under atmospheric pressure with a palladised barium sulphate catalyst gave a monobromo-compound. *X*-Ray crystallographic examination of this material by Mr. M. M. Woolfson of the Cavendish Laboratory showed that it was clearly 5′-bromo-3′ : 5′-dideoxythymidine (I; R = H, R′ = Br) (see Figure). Prolonged hydrogenation gave a small yield of 3′ : 5′-dideoxythymidine (I; R = R′ = H), although under the conditions employed some breakdown to thymine occurred. It should be noted that in these experiments replacement of a secondary sulphonyloxy-group in a nucleoside derivative by halogen occurred readily. This ease of replacement is probably to be ascribed to the absence of a hydroxyl group at position 2′ in the deoxyribonucleosides (cf. Matheson and Angyal, *J.*, 1952, 1133).

Methanesulphonylation of 5′-tritylthymidine gave 3′-methanesulphonyl-5′-tritylthymidine (I; R = O·SO_2·Me, R′ = O·CPh_3) from which, by heating with 80% acetic acid, 3′-

* Part IV, *J.*, 1954, 1882.

methanesulphonylthymidine (I; R = O·SO_2·Me, R′ = OH) was obtained. Treatment of the ether ester (I; R = O·SO_2·Me, R′ = O·CPh_3) with lithium bromide under the usual conditions gave 3′-bromo-3′-deoxy-5′-tritylthymidine (I; R = Br, R′ = O·CPh_3), and with sodium iodide 3′-deoxy-3′-iodo-5′-tritylthymidine (I; R = I, R′ = O·CPh_3) was similarly obtained; the latter gave 3′-deoxy-3′-iodothymidine (I; R = I, R′ = OH) which was smoothly reduced to 3′-deoxythymidine (I; R = H, R′ = OH).

5′-Bromo-3′ : 5′-dideoxythymidine.

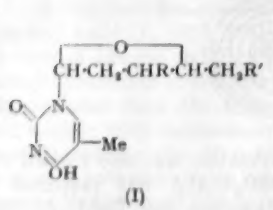


A comparable series of reactions leading to 5′-deoxythymidine was also carried out. 5′-Toluene-*p*-sulphonylthymidine (I; R = OH, R′ = O·SO_2·C_7H_7) was prepared by deacetylating 3′-acetyl-5′-toluene-*p*-sulphonylthymidine (Michelson and Todd, *J.*, 1953, 951); when heated with sodium iodide it gave 5′-deoxy-5′-iodothymidine (I; R = OH, R′ = I) which underwent ready reduction to 5′-deoxythymidine (I; R = OH, R′ = H). When lithium bromide was used instead of sodium iodide the ester (I; R = OH, R′ = O·SO_2·C_7H_7) gave 5′-bromo-5′-deoxythymidine (I; R = OH, R′ = Br) which, like the other deoxyhalogenothymidines, was dimorphic. *X*-Ray crystallographic examination of the compound (I; R = OH, R′ = Br) by Dr. W. Cochran and Mr. M. Huber of the Cavendish Laboratory confirmed the correctness of the structure assigned and also showed conclusively the β-configuration at the glycosidic centre; these results, incidentally, establish conclusively the correctness of the structures assigned to the intermediates employed in the synthesis of the thymidine mononucleotides (Michelson and Todd, *loc. cit.*).

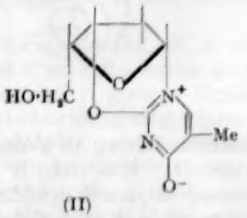
As expected, 3′-acetyl-5′-deoxy-5′-iodothymidine with silver dibenzyl phosphate yielded a product from which, by removal of protecting groups, thymidine-5′ phosphate was obtained; this was identified by comparison with an authentic specimen (Michelson and Todd, *loc. cit.*). Phosphorylation of 5′-deoxy-5′-iodothymidine with dibenzyl phosphorochloridate gave a good yield of 5′-deoxy-5′-iodothymidine-3′ dibenzyl phosphate.

As a preliminary to the above experiments on the replacement of iodine atoms in deoxyiodothymidine derivatives by dibenzyl phosphate residues their reaction with silver acetate in methyl cyanide was examined. To our surprise 3′-deoxy-3′-iodothymidine (I; R = I, R′ = OH), although it reacted readily enough with silver acetate on being heated in this medium did not yield the expected 3′-acetylthymidine. Instead, a crystalline high-melting substance $C_{10}H_{12}O_4N_2$ was obtained. A similar experiment with 5′-deoxy-5′-iodothymidine gave a crystalline isomeric compound $C_{10}H_{12}O_4N_2$ as main product, although a certain amount of 5′-acetylthymidine was also produced. 3′-Acetyl-5′-deoxy-5′-iodothymidine gave with silver acetate in the same way a substance $C_{12}H_{14}O_5N_2$ accompanied by a small amount of a second product which, from its paper chromatographic behaviour, was almost certainly 3′ : 5′-diacetylthymidine. In these initial experiments the solvent employed was a laboratory sample of methyl cyanide which had not been specially purified. With highly purified, dry methyl cyanide, no reaction occurred. It was ultimately found that the presence of traces of aliphatic amines in the methyl cyanide originally used was essential and that when purified methyl cyanide was used it was necessary to add a small amount of, *e.g.*, diethylamine.

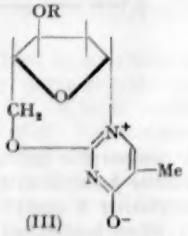
In previous papers we described the formation of *cyclo*nucleoside salts by heating the 5′-toluene-*p*-sulphonates of adenosine and cytidine (Clark, Todd, and Zussman, *J.*, 1951, 2952) or of deoxyadenosine and deoxycytidine (Andersen, Hayes, Michelson, and Todd, *J.*, 1954, 1882) in inert solvents. The easy formation of these salts by intramolecular alkylation was doubtless due in part to the markedly basic nature of the purine and pyrimidine derivatives involved. Nevertheless, if thymidine also has the β-configuration at the glycosidic linkage, it might well be that treatment of suitable deoxyiodothymidine derivatives with silver acetate could also yield analogous *cyclo*nucleoside derivatives. The properties of the products described above, and in particular their ultra-violet absorption spectra, lend strong support to this view. All three compounds show an absorption maximum at 250 mμ in place of the characteristic thymidine maximum at 268 mμ, the shift being very similar to that observed in passing from cytidine (max. 270 mμ) to O^2 : 5′-*cyclo*cytidine toluene-*p*-sulphonate (max. 252—253 mμ). The infra-red spectra of these three compounds are in accord with their formulation as O^2 : 3′-*cyclo*thymidine (II), O^2 : 5′-*cyclo*thymidine (III; R = H), and 3′-acetyl-O^2 : 5′-*cyclo*thymidine (III; R = Ac).



(I)



(II)



(III)

The cyclisation between position 3′ and the oxygen attached to $C_{(2)}$ in the pyrimidine ring which is postulated in (II) presents no steric difficulty; on the evidence of molecular models it seems to be even easier than the closure postulated in (III) and, indeed, this accords with the observed ease of formation of the compounds and their relative stabilities. A change of configuration at position 3′ appears to be involved (and may have occurred during the preparation of the 3′-iodo-derivative), so that (II) is a derivative of 2-deoxy-D-xylose rather than of 2-deoxy-D-ribose. In any case it should be noted that the acceptance of structures (II) and (III) requires the formulation of thymidine as a β-2-deoxy-D-ribofuranoside since cyclisation could not take place if it were an α-glycoside.

In view of the ready cyclisation of 3′-deoxy-3′-iodothymidine, the effect of alkali on the sulphonyl derivatives of thymidine was examined. While 5′-toluene-*p*-sulphonylthymidine is quite stable, treatment of 3′ : 5′-dimethanesulphonylthymidine with ethanolic ammonia under mild conditions gave a good yield of the highly crystalline 5′-methane-

sulphonyl-O^2 : 3′-*cyclo*thymidine, inversion at position 3′ occurring with elimination of one molecule of methanesulphonic acid, to give a derivative of 2-deoxy-D-xylose.

The behaviour of the cylic compounds (II) and (III; R = H) when subjected to alkaline and acid hydrolysis is of interest. Both compounds are hydrolysed by 0·1N-aqueous sodium hydroxide or ammonia at room temperature, reaction being much the faster with (III; R = H). The product from (III; R = H) was identified as thymidine. That from (II) was very similar to, but apparently not identical with, thymidine; although not rigidly identified it is believed to be the isomeric thymine 2-deoxy-D-xylofuranoside. Towards acid the compounds were more stable; (II) was unaffected and (III; R = H) was only slowly attacked by 0·1N-hydrochloric acid at room temperature. At 100° there was in each case rapid hydrolysis, first to a substance similar in its chromatographic behaviour to thymidine and apparently containing the pyrimidine system (ultra-violet absorption) and the deoxy-sugar residue (cysteine spray), and then by further action of the acid to thymine and a free deoxy-sugar. The sugar obtained in this way from (III; R = H) appeared to be 2-deoxy-D-ribose but that from (II) differed in its R_F value on paper chromatograms. Although lack of material has prevented actual isolation of the sugar from (II) comparison of its paper chromatographic behaviour with that of authentic 2-deoxy-D xylose leaves little room for doubt as to its identity with this substance. It should be noted that thymidine itself is unaffected by 0·1N-sodium hydroxide and only very slightly by 0·1N-hydrochloric acid under the conditions used in these hydrolyses.

The results of the above hydrolyses can be satisfactorily explained on the basis of structures (II) and (III; R = H) if it be assumed that alkaline hydrolysis splits the linkage between the oxygen attached to $C_{(2)}$ and the pyrimidine residue, yielding thymidine from (III; R = H) and the isomeric 2-deoxy-D-xyloside from (II), and that acid effects cleavage at $N_{(3)}$ in the pyrimidine system in the first instance, giving deoxy-sugars attached to the thymine residue at $C_{(2)}$ by an ether linkage which can be hydrolysed further to yield thymine and free deoxy-sugars.

Experimental

3′ : 5′-*Dimethanesulphonylthymidine*.—Methanesulphonyl chloride (6 c.c.) was added to a solution of thymidine (5 g.) in dry pyridine (60 c.c.) at 0°, and the mixture kept at 0° overnight. Ice-water (4 c.c.) was added, the mixture kept at 0° for 1 hr., then poured into ice-water (800 c.c.) with vigorous stirring, and kept at 0° for several hours. The crystalline precipitate of 3′ : 5′-*dimethanesulphonyl thymidine* (7·55 g.) was collected and dried. Recrystallised from 90% ethanol it formed colourless needles, m. p. 168—169° (decomp.) (Found, in material dried for 15 hr. at 60°/10^{-3} mm.: C, 36·4; H, 4·6; N, 7·0. $C_{12}H_{18}O_9N_2S_2$ requires C, 36·2; H, 4·5; N, 7·0%).

5′-*Deoxy*-5′-*iodo*-3′-*methanesulphonylthymidine*.—A solution of 3′ : 5′-dimethanesulphonyl thymidine (3·5 g.) and sodium iodide (3·5 g.) in dry acetone (40 c.c.) was heated at 100° for 2 hr. Sodium methanesulphonate was removed and the filtrate evaporated to dryness. Water (50 c.c.) was added, the mixture shaken well, and the pale yellow amorphous solid collected. Several recrystallisations, first from ethanol and finally from water, gave needles of 5′-*deoxy*-5′-*iodo*-3′-*methanesulphonylthymidine* (1·84 g.), m. p. 161—162° (decomp.) (Found, in material dried at 80°/10^{-3} mm. for 6 hr.: C, 30·6; H, 3·6; N, 6·4. $C_{11}H_{15}O_6SN_2I$ requires C, 30·7; H, 3·5; N, 6·5%).

3′ : 5′-*Dibromo*-3′ : 5′-*dideoxythymidine*.—A solution of 3′ : 5′-dimethanesulphonylthymidine (1 g.) and lithium bromide (1 g.) in anhydrous acetone (10 c.c.) was heated at 100° for 2 hr. Lithium methanesulphonate (0·47 g.; theor., 0·51 g.) was collected and the filtrate taken to dryness under reduced pressure. The residue was well washed with water and recrystallised twice from ethanol, giving the product (0·17 g.) as needles, m. p. 159° (decomp.) (Found, in material dried for 12 hr. at 60°/10^{-3} mm.: C, 33·2; H, 3·4; N, 7·4. $C_{10}H_{12}O_3N_2Br_2$ requires C, 32·6; H, 3·3; N, 7·6%).

5′-*Bromo*-3′ : 5′-*dideoxythymidine*.—A solution of 3′ : 5′-dibromo-3′ : 5′-dideoxythymidine (0·6 g.) in aqueous ethanol was hydrogenated in the usual way with palladised barium sulphate at pH 9. Catalyst was removed and the filtrate taken to small volume under reduced pressure. The 5′-*bromo*-3′ : 5′-*dideoxythymidine* which separated was collected (0·4 g.) and recrystallised twice from ethanol, forming needles, m. p. 155—156° (Found, in material dried at 100°/10^{-3} mm. for 12 hr.: C, 41·4; H, 4·4; N, 9·9. $C_{10}H_{13}O_3N_2Br$ requires C, 41·5; H, 4·5; N, 9·7%). A solution of 5′-bromo-3′ : 5′-dideoxythymidine (100 mg.) in aqueous ethanol (10 c.c. of 50%)

at pH 9 with ammonium hydroxide was hydrogenated at atmospheric temperature and pressure during 24 hr. with palladised barium sulphate. Catalyst was removed and the filtrate taken to dryness under reduced pressure. The residue was extracted twice with hot ethyl acetate, leaving a residue of thymine and ammonium bromide. The ethyl acetate extracts were taken to dryness, the residue was triturated with 1 : 1 ether–light petroleum (b. p. 40—60°), and the mixture kept at 0° for several hours. The crystalline deposit was recrystallised from ether–light petroleum (b. p. 60—80°) and finally sublimed at $120°/10^{-1}$ mm., giving crude 3′ : 5′-dideoxythymidine (40 mg.) as needles, m. p. 105°, still contaminated with a trace of 5′-bromo-3′ : 5′-dideoxythymidine (Found: C, 55·0; H, 6·1. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7%).

3′-Methanesulphonyl-5′-tritylthymidine.—Methanesulphonyl chloride (2·5 c.c.) was added to a solution of 5′-tritylthymidine (5 g.) in pyridine (50 c.c.), and the mixture kept at 0° overnight, with exclusion of moisture. Ice-water (1 c.c.) was then added and after 1 hr. at 0° the mixture was poured into ice-water (500 c.c.) with vigorous stirring. The precipitate of *3′-methanesulphonyl-5′-tritylthymidine* was filtered off, well washed with water, and dried (5·4 g.) (Found, in material dried for 15 hr. at $60°/10^{-3}$ mm.: C, 63·9; H, 5·6; N, 5·0. $C_{30}H_{30}O_7N_2S$ requires C, 64·1; H, 5·3; N, 5·0%).

3′-Methanesulphonylthymidine.—A solution of 3′-methanesulphonyl-5′-tritylthymidine (3·9 g.) in 80% acetic acid (40 c.c.) was heated under reflux for 6 min. Acetic acid was then removed under reduced pressure and the residue shaken repeatedly with ether to remove triphenylmethanol. The ether-insoluble residue was recrystallised from hot water; *3′-methanesulphonylthymidine* crystallised in needles (1·1 g.), m. p. 116° (Found, in material dried at $80°/10^{-3}$ mm. for 12 hr.: C, 41·2; H, 5·4; N, 9·0. $C_{11}H_{16}O_7N_2S$ requires C, 41·3; H, 5·0; N, 8·8%).

3′-Bromo-3′-deoxy-5′-tritylthymidine.—A solution of 3′-methanesulphonyl-5′-tritylthymidine (1 g.) and lithium bromide (1 g.) in anhydrous acetone (10 c.c.) was heated at 100° for 2 hr. Lithium methanesulphonate (0·15 g.; theory, 0·18 g.) was removed and the filtrate taken to dryness under reduced pressure. Water (40 c.c.) was added to the residue, the mixture shaken vigorously, and the amorphous solid collected, washed well with water, and dried (0·9 g.). Recrystallised first from methanol and then from acetone–methanol, *3′-bromo-3′-deoxy-5′-tritylthymidine* formed cubes, m. p. 144° (Found, in material dried for 12 hr. at $60°/10^{-3}$ mm.: C, 63·5; H, 5·1; N, 5·3. $C_{29}H_{27}O_4N_2Br$ requires C, 63·6; H, 4·9; N, 5·1%).

3′-Deoxy-3′-iodo-5′-tritylthymidine.—A solution of 3′-methanesulphonyl-5′-tritylthymidine (6 g.) and sodium iodide (3·5 g.) in anhydrous acetone (50 c.c.) was heated at 100° for 2 hr. Sodium methanesulphonate (1·11 g.; theory, 1·26 g.) was removed and the filtrate taken to dryness under reduced pressure, water (100 c.c.) added to the residue, and the mixture shaken vigorously. The yellow amorphous solid was collected, well washed with water, and dried (6·0 g.). Recrystallised from methanol and then from acetone–methanol, *3′-deoxy-3′-iodo-5′-tritylthymidine* formed colourless cubes, m. p. 147° (Found, in material dried for 12 hr. at $60°/10^{-3}$ mm.: C, 58·8; H, 5·0; N, 4·8. $C_{29}H_{27}O_4N_2I$ requires C, 58·6; H, 4·5; N, 4·7%).

3′-Deoxy-3′-iodothymidine.—A solution of 3′-deoxy-3′-iodo-5′-tritylthymidine (5·0 g.) in 80% acetic acid (35 c.c.) was heated under reflux for 7 min. Acetic acid was removed under reduced pressure and the residue shaken several times with ether to remove triphenylmethanol. The ether-insoluble residue was recrystallised twice from water, giving 3′-deoxy-3′-iodothymidine as needles (1·0 g.), m. p. 166—167° (decomp.) (Found, in material dried for 6 hr. at $90°/10^{-3}$ mm.: C, 34·8; H, 3·7; N, 7·7. $C_{10}H_{13}O_4N_2I$ requires C, 34·1; H, 3·7; N, 7·9%).

3′-Deoxythymidine.—A solution of 3′-deoxy-3′-iodothymidine (0·5 g.), in aqueous ethanol brought to pH 10 with ammonia, was hydrogenated at atmospheric temperature and pressure with palladised barium sulphate. When hydrogenation was complete (*ca.* 3 hr.) catalyst was removed and the filtrate taken to dryness under reduced pressure below 30°. The residue was extracted several times with hot ethyl acetate, and the combined ethyl acetate extracts were taken to small volume and cooled. *3′-Deoxythymidine* separated as needles, m. p. 145° (0·2 g.), and was recrystallised twice from acetone–light petroleum (b. p. 40—60°) without change in m. p. (Found, in material dried at $90°/10^{-3}$ mm. for 6 hr.: C, 53·3; H, 6·5; N, 12·2. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4%).

5′-Toluene-p-sulphonylthymidine.—A solution of 3′-acetyl-5′-toluene-*p*-sulphonylthymidine (Michelson and Todd, *J.*, 1953, 951) (9·7 g.) in methanol half saturated with ammonia (75 c.c.) was kept at 0° overnight. Methanol was removed under reduced pressure and the crystalline residue of *5′-toluene-p-sulphonylthymidine* recrystallised from methanol as needles (6·5 g.), m. p. 172° (decomp.) (Found, in material dried for 15 hr. at $80°/10^{-3}$ mm.: C, 51·6; H, 5·3; N, 6·9. $C_{17}H_{20}O_7N_2S$ requires C, 51·5; H, 5·1; N, 7·1%).

5′-Deoxy-5′-iodothymidine.—A solution of 5′-toluene-*p*-sulphonylthymidine (5·326 g.) and

sodium iodide (5 g.) in acetone (20 c.c.) was heated at 100° for 2 hr. Sodium toluene-*p*-sulphonate (2·59 g.; theory, 2·60 g.) was removed and the filtrate taken to dryness under reduced pressure. Water (40 c.c.) was added to the residue, and the resultant crystalline mass collected, washed with water, and dried [4·6 g.; m. p. 172° (decomp.)]. Recrystallised from water, *5′-deoxy-5′-iodothymidine* formed needles, m. p. 168° (decomp.) (Found, in material dried for 12 hr. at 60°/10^{-3} mm.: C, 34·2; H, 3·6; N, 7·9. $C_{10}H_{13}O_4N_2I$ requires C, 34·1; H, 3·7; N, 7·9%).

5′-Deoxythymidine.—A solution of 5′-deoxy-5′-iodothymidine (0·6 g.) in aqueous ethanol at pH 10 (ammonia) was hydrogenated with palladised barium sulphate. When hydrogenation was complete, catalyst was removed and washed with hot ethanol, and the combined filtrate and washings were taken to small volume; *5′-deoxythymidine* crystallised (0·250 g.). Recrystallised from ethanol it had m. p. 188° (Found, in material dried at 90°/10^{-3} mm. for 6 hr.: C, 53·3; H, 6·1; N, 12·3. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4%).

5′-Bromo-5′-deoxythymidine.—A solution of 5′-toluene-*p*-sulphonylthymidine (0·50 g.) and lithium bromide (0·50 g.) in anhydrous acetone (5 c.c.) was heated at 100° for 2 hr. Acetone was removed under reduced pressure, water (20 c.c.) added to the residue, and the resultant crystalline mass collected, washed with water, and dried [0·335 g.; m. p. 154° (decomp.)]. Recrystallised twice from water, *5′-bromo-5′-deoxythymidine* formed needles, m. p. 129° (decomp.) (Found, in material dried for 12 hr. at 60°/10^{-3} mm.: C, 38·8; H, 4·3; N, 9·2. $C_{10}H_{13}O_4N_2Br$ requires C, 39·3; H, 4·3; N, 9·2%).

Action of Silver Dibenzyl Phosphate on 3′-Acetyl-5′-deoxy-5′-iodothymidine.—A mixture of silver dibenzyl phosphate (100 mg.) and 3′-acetyl-5′-deoxy-5′-iodothymidine (100 mg.) in dry benzene (15 c.c.) was refluxed with stirring for 2 hr. Silver iodide was removed by filtration, the benzene solution washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4), and solvent removed under reduced pressure to give a colourless gum. This was dissolved in aqueous ethanol, hydrogenated with a palladium catalyst, the acetyl group removed by treatment with barium hydroxide solution, and the nucleotide worked up as previously described (Michelson and Todd, *J.*, 1953, 951), giving barium thymidine-5′ phosphate (55 mg.) identical with authentic material.

5′-Deoxy-5′-iodothymidine-3′ Dibenzyl Phosphate.—A solution of anhydrous 5′-deoxy-5′-iodothymidine (1 g.) in dry pyridine (20 c.c.) at −30° was treated with dibenzyl phosphorochloridate (from 3 g. of dibenzyl phosphite), and the mixture kept just above its f. p. for 6 hr. and then at 0° overnight. Sodium carbonate (1·5 g.) and water (10 c.c.) were added, and the mixture was taken to dryness under reduced pressure. To the residue water and chloroform were added and the chloroform extract was washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4). Solvent was removed under reduced pressure and the residual gum taken to dryness twice with ethanol, then dissolved in acetone (5 c.c.), a 1 : 1 mixture (100 c.c.) of ether and light petroleum (b. p. 40—60°) was added, and the solution kept at 0° overnight. The supernatant liquid was decanted from the gelatinous mass which had separated and the precipitation repeated. The final gel was dissolved in acetone and taken to a glass under reduced pressure (yield, 1·1 g.). For analysis the gum was dissolved in acetone, and the solution filtered and poured into water, giving *5′-deoxy-5-iodothymidine-3′ dibenzyl phosphate* as a white amorphous solid (Found, in material dried at room temp./1 mm. for 2 weeks: C, 47·6; H, 4·6; N, 4·2. $C_{24}H_{26}O_7N_2PI$ requires C, 47·1; H, 4·3; N, 4·6%).

Paper Chromatography of Deoxythymidine Derivatives.—Whatman No. 1 paper. Solvent system, *n*-butanol–water (86 : 14) in ascending chromatograms. Cysteine spray (Buchanan, *Nature*, 1951, **168**, 1091). The results are tabulated.

	R_F	Cysteine spray colour
3′-Methanesulphonylthymidine	0·46	Pink
3′-Deoxy-3′-iodothymidine	0·71	Pink
3′-Deoxythymidine	0·53	Faint yellow
5′-Bromo-5′-deoxythymidine	0·66	Pink
5′-Deoxy-5′-iodothymidine	0·67	Pink
5′-Deoxythymidine	0·56	Brown
5′-Toluene-*p*-sulphonylthymidine	0·70	Pink
3′ : 5′-Dibromo-3′ : 5′-dideoxythymidine	0·79	Pink
5′-Bromo-3′ : 5′-dideoxythymidine	0·71	Faint yellow
Thymidine	0·40	Pink
2-Deoxyribose	0·27	Pink
2-Deoxyxylose	0·30	Pink

5′-Methanesulphonyl-O^2 : 3′-cyclothymidine.—Saturated methanolic ammonia (5 c.c.) was added to a solution of 3′ : 5′-dimethanesulphonylthymidine (0·13 g.) in 90% ethanol (5 c.c.), and the mixture kept at room temperature overnight. The crystalline deposit was collected and

recrystallised from 90% ethanol, giving *5′-methanesulphonyl* O²: 3′-cyclo*thymidine* as needles, m. p. 176° (decomp.) (0·08 g.) (Found, in material dried for 12 hr. at 100°/1 mm.: C, 43·7; H, 4·5; N, 9·3. $C_{11}H_{14}O_6N_2S$ requires C, 43·7; H, 4·6; N, 9·3%). Light absorption in H_2O: max. 250—252, min. 218 mμ.

O²: 3′-cyclo*Thymidine*.—A solution of 3′-deoxy-3′-iodothymidine (200 mg.) in dry laboratory-grade methyl cyanide (25 c.c.) was heated and stirred under reflux with powdered silver acetate (400 mg.) for 1½ hr. The solution was filtered hot, hydrogen sulphide was passed through the filtrate to remove silver ions, and, after further filtration, the solution was evaporated under reduced pressure. The residue was extracted with hot ethanol and the filtered extract concentrated to small bulk and cooled. O²: 3′-cyclo*Thymidine* separated as colourless needles (110 mg.); recrystallised from 90% ethanol it had m. p. 230° (Found, in material dried for 12 hr. at 100°/10^{-3} mm.: C, 53·8; H, 5·7; N, 12·3. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). Light absorption: in H_2O, max. 252 (ε 7900), min. 220 (ε 4900); in N/100-HCl, max. 254 (ε 7800), min. 220 (ε 4900); in N/100-NaOH, max. 254 (ε 7800), min. 219 (ε 4900). Thymidine itself had the following light absorption: in H_2O, max. 269 (ε 9300), min. 235 mμ (ε 1900); in N/100-HCl, max. 267—268 (ε 9200), min. 235 (ε 1900); in N/100-NaOH, max. 266 (ε 7200), min. 243 mμ (ε 4200).

O²: 5′-cyclo*Thymidine*.—5′-Deoxy-5′-iodothymidine (500 mg.) in methyl cyanide (45 c.c.) was refluxed and stirred for 1½ hr. with silver acetate (750 mg.). Working up as described above gave an ethanolic solution which deposited O²: 5′-cyclo*thymidine*, which recrystallised from 90% ethanol as colourless needles (100 mg.), m. p. 230° (on one occasion m. p. 218°) (Found, in material dried 12 hr. at 100°/10^{-3} mm.: C, 53·3; H, 5·8; N, 12·1. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). Light absorption: in H_2O, max. 250—253 (ε 10,400), min. 218 mμ (ε 3500); in N/100-HCl, max. 251—252 (ε 9000), min. 219 (ε, 4000); in N/100-NaOH, max. 252 (ε 10,400), min. 219 mμ (ε 5600).

5′-Acetylthymidine.—Paper-chromatographic examination of the mother-liquor from the first crystallisation of *O²: 5′-cyclo*thymidine showed the presence of a material with a considerably higher R_T value. The mother-liquor was therefore taken to dryness, the residue dissolved in acetone, and ether was added to slight turbidity. The mixture was set aside at 0° overnight, the clear solution decanted from deposited gum, and light petroleum (b. p. 40—60°) added to slight turbidity. During several days at 0° colourless needles of *5′-acetylthymidine* separated, which recrystallised from acetone–light petroleum (b. p. 40—60°) as needles (50 mg.), m. p. 146° (Found, in material dried for 8 hr. at 90°/10^{-3} mm.: C, 50·5; H, 5·8; N, 10·1. $C_{12}H_{16}O_6N_2$ requires C, 50·7; H, 5·6; N, 9·9%).

3′: 5′-*Diacetylthymidine*.—A solution of thymidine (1 g.) in dry pyridine (15 c.c.) and acetic anhydride (5 c.c.) was kept at room temperature for 15 hr., then poured into ice-water (150 c.c.). The aqueous solution was extracted thrice with chloroform, and the combined extracts were washed successively with ice-cold dilute sulphuric acid, sodium hydrogen carbonate, and water, then dried (Na_2SO_4) and evaporated. The residue, which crystallised on trituration with dry ether, was recrystallised from ethanol, giving 3′: 5′-*diacetylthymidine* (1·1 g.) as colourless prisms, m. p. 125° (Found, in material dried for 8 hr. at 80°/10^{-3} mm.: C, 51·7; H, 5·7; N, 8·7. $C_{14}H_{18}O_7N_2$ requires C, 51·5; H, 5·5; N, 8·6%).

3′-*Acetyl*-O²: 5′-cyclo*thymidine*.—A solution of 3′-acetyl-5′-deoxy-5′-iodothymidine (500 mg.) in laboratory-grade methyl cyanide (25 c.c.) was stirred and refluxed with silver acetate for 1½ hr., then worked up as described above for analogous experiments. 3′-*Acetyl*-O²: 5′-cyclo*thymidine* (125 mg.), crystallised from 90% ethanol, had m. p. 252° (Found, in material dried for 12 hr. at 100°/10^{-3} mm.: C, 54·1; H, 5·0; N, 11·0. $C_{12}H_{14}O_5N_2$ requires C, 54·1; H, 5·3; N, 10·5%). Light absorption: in 50% EtOH, max. 249—250 (ε 11,000), min. 220 (ε 3600); in N/100-HCl, max. 248—249 (ε 10,700), min. 218 (ε 3700); in N/100-NaOH, max. 248—249 (ε 10,500), min. 218 mμ (ε 3500).

Paper chromatography showed the presence of a faster-running material [R_T 0·63 in *n*-butanol–water (86 : 14)] in the mother-liquor from the first crystallisation of 3′-acetyl-O²: 5′-*cyclo*thymidine; although it was not isolated this material is believed to be 3′: 5′-diacetylthymidine since this showed an identical R_T (0·63) when run alongside it.

Paper Chromatography of cyclo*Thymidines*.—Ascending chromatograms, Whatman No. 1 paper. Solvent systems: A, *n*-butanol–water (86 : 14); B, *iso*propanol–water–concentrated aqueous ammonia (70 : 20 : 10); C, *n*-propanol–2N-HCl (3 : 1). R_T values found were:

	A	B	C
Thymidine	0·39	0·57	0·74
O²: 3′-*cyclo*Thymidine	0·22	0·61	0·46
O²: 5′-*cyclo*Thymidine	0·23	0·59	0·96
3′-Acetyl-O²: 5′-*cyclo*thymidine	0·39	0·62	0·89

Paper Electrophoresis of Some Thymidine Derivatives.—Whatman No. 1 paper at 220 v. Movements (cm.), towards negative pole in all cases, were :

	N/10-AcOH, 6 hr.	N/10-NH_3, 7 hr.
Thymidine	0·8	0·0
5′-Deoxythymidine	0·5	0·3
O^2 : 3′-*cyclo*Thymidine	0·7	2·5
O^2 : 5′-*cyclo*Thymidine	0·8	2·3
3′-Acetyl-O^2 : 5′-*cyclo*thymidine	0·5	2·3

Hydrolysis of O^2 : 3′-cyclo*Thymidine and* O^2 : 5′-cyclo*Thymidine.*—(a) ***With 0·1N-sodium hydroxide.*** After 2 hr. at room temperature partial hydrolysis of the 3′-compound had occurred, giving a compound travelling exactly like thymidine on paper chromatograms; the 5′-compound had undergone complete hydrolysis to a similar product. Hydrolysis of the 3′-compound was nearly complete after 24 hr.

The hydrolysis product from both compounds ran almost exactly like thymidine on paper chromatograms in *n*-butanol–water, *iso*propanol–ammonia, or *n*-propanol–hydrochloric acid and gave a strong cysteine spray colour only on the area showing ultra-violet absorption. The ultra-violet absorption of the product was identical with that of natural thymidine (comparison of $\lambda_{max.}$, $\lambda_{min.}$, and optical density ratios 250/260 and 280/260 mμ both in N/20-acid and N/20-alkali).

Closer examination of the alkaline hydrolysis, with dilute ammonia as reagent, showed that the product from O^2 : 5′-*cyclo*thymidine was in fact thymidine (infra-red spectrum, m. p., and mixed m. p.). O^2 : 3′-*cyclo*Thymidine, however, gave a product moving slightly faster (R_T 0·41) than thymidine (R_T 0·40) in paper chromatograms (*n*-butanol–water). The infra-red spectrum of this material was similar to, but not identical with, that of thymidine; scarcity of material prevented thorough study of the product but it is almost certainly the expected thymine 2-deoxy-D-xylofuranoside.

(b) *With 0·1N-hydrochloric acid.* After 48 hr. at room temperature the 3′-compound was unchanged and only slight hydrolysis had occurred with the 5′-compound.

After 10 minutes at 100° the 3′-compound was almost completely converted into a faster-moving substance with the same R_T as thymidine in *n*-butanol–water, showing ultra-violet absorption and a strong cysteine spray reaction, together with a smaller amount of a substance revealed on paper chromatograms as a spot with a weak cysteine spray reaction and no ultra-violet absorption (R_T/R_T of thymidine = 0·75). On similar treatment the 5′-compound was completely destroyed, yielding a substance with the same R_T as thymidine (or thymine) in *n*-butanol–water, giving a weak cysteine spray reaction, and another travelling on paper chromatograms as a spot devoid of ultra-violet absorption but with a strong cysteine spray reaction (R_T/R_T of thymidine = 0·67).

After 30 minutes the 3′-compound was completely converted into one ultra-violet-absorbing substance with greatly decreased cysteine spray reaction, the non-absorbing cysteine spray-positive substance having correspondingly increased in amount. With the 5′-compound the cysteine spray reaction of the material showing ultra-violet absorption was very weak indeed.

After 1 hr. at 100° both compounds appeared to have been hydrolysed completely, giving a product with ultra-violet absorption and another with a cysteine spray reaction. The material showing ultra-violet absorption was identified in each case as thymine by paper chromatography in 3 solvent systems, by measurement of ultra-violet absorption ($\lambda_{max.}$, $\lambda_{min.}$, and optical density ratios at 250/260 and 280/260 mμ in N/20-acid and -alkali), and by isolation in crystalline form. The cysteine spray-positive product from the 5′-compound agreed in paper-chromatographic behaviour with 2-deoxy-D-ribose (R_T/R_T thymidine = 0·67) and that from the 3′-compound with 2-deoxy-D-xylose (R_T/R_T thymidine = 0·75) (both sugars treated with N/10-hydrochloric acid for 1 hr. at 100°).

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Rearrangement of 2 : 4-Xylyl Hydrogen Maleate.

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The rearrangement of 2 : 4-xylyl hydrogen maleate with aluminium chloride is discussed.

Baddeley, Makar, and Ivinson (*J.*, 1953, 3969) have shown that 2 : 4 : 1-xylenol and maleic anhydride in the presence of aluminium chloride yield β-(2-hydroxy-3 : 5-dimethylbenzoyl)acrylic acid (I; R = H). We had previously and unsuccessfully attempted to prepare this acid by Fries rearrangement (cf. Cocker, *J.*, 1946, 30; Cocker, Fateen, and Lipman, *J.*, 1951, 929) of 2 : 4-xylyl hydrogen maleate (II). In fact, when this ester was heated with aluminium chloride at 145°, the product was 4-hydroxy-5 : 7-dimethyl-3-oxoindane-1-carboxylic acid (III) identified by comparison with the product of the action of a mixture of aluminium chloride and sodium chloride on the aroylacrylic acid (I; R = H) (cf. Baddeley, Makar, and Ivinson, *loc. cit.*; personal communication from Dr. Baddeley). When however the ester (II) was heated with aluminium chloride in boiling tetrachloroethane (cf. Smith and Holmes, *J. Amer. Chem. Soc.*, 1951, **73**, 3847), a second isomeric acid was also obtained which unlike (III) gave no ferric reaction. The properties of this acid make it clear that it is 6 : 8-dimethyl-4-oxochroman-2-carboxylic acid (IV), and not the isomeric acid (V) (cf. Dann and Mylius, *Annalen*, 1954, **587**, 7). Thus the spectrum of the chroman acid (IV), as expected, is almost identical with that of the indane acid (III), whereas (V) would be expected to exhibit light absorption similar to the saturated esters of 2 : 4 : 1-xylenol.

Substance	$\lambda_{max.}$ (in EtOH)	log ε
(III)	2170, 2620, 3350Å	4·31, 4·12, 3·76
(IV)	2170, 2590, 3420	4·53, 4·10, 3·75
2 : 4-Xylyl chloroacetate	2650, 2730	3·02, 2·98
2 : 4-Xylyl hydrogen succinate	2675, 2730	2·72, 2·69

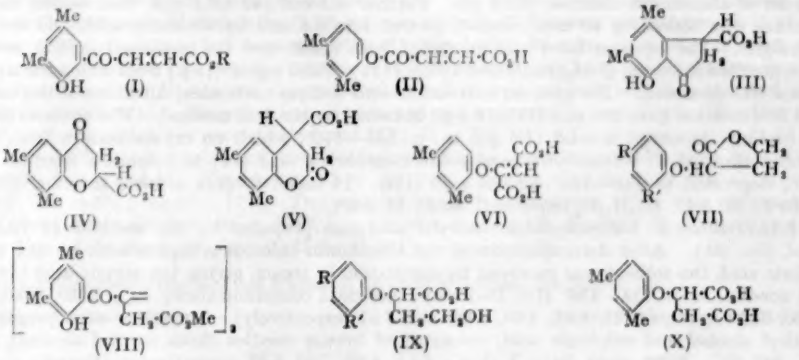
Moreover the methyl ester of (IV) is produced when methyl β-(2-hydroxy-3 : 5-dimethylbenzoyl)acrylate (I; R = Me) is treated in the cold with tripropylamine in presence of five equivalents of diethyl malonate. The base-catalysed addition of the hydroxyl group of the phenol (I; R = Me) to the double bond is not unexpected, but eliminates structure (V) for the product. Diethyl malonate in excess is apparently essential for this reaction, the active anion $-CH(CO_2Et)_2$ presumably being the catalyst (cf. Pepper, *Quart. Rev.*, 1954, **8**, 88). In absence of malonic ester the product is a dimer of (I; R = Me): the ferric reaction and spectrum of this product, both similar to those of the starting ester (I; R = Me), and its low reactivity towards hydrogen and hydrogen bromide in acetic acid, suggest that it is probably (VIII).

We have been unable to prepare 2 : 4-dimethylphenoxysuccinic acid (X) from which 6 : 8-dimethyl-4-oxochroman-2-carboxylic acid (IV) could have been produced. Reduction of 2 : 4-dimethylphenoxyfumaric acid (VI) (Baddeley, Makar, and Ivinson, *loc. cit.*) was unsuccessful by catalytic methods, whilst sodium amalgam gave mainly 2 : 4 : 1-xylenol. The diethyl ester of (VI) was also unchanged by hydrogen in presence of palladised charcoal, whilst in presence of platinic oxide the aromatic ring suffered reduction.

Oxidation of α-2 : 4-dimethylphenoxy-γ-butyrolactone (VII; R = R′ = Me), obtained from 2 : 4 : 1-xylenol and α-bromo-γ-butyrolactone, with chromium trioxide (cf. Julia, *Bull. Soc. chim.*, 1954, 471) gave an intractable gum, and with permanganate gave a product which had properties consistent with its formulation as (IX; R = Me, R′ = CO_2H, or *vice versa*). When heated above its melting point, or with sulphuric acid, the oxidation product gave a lactone (VII; R = Me, R′ = CO_2H, or *vice versa*).

Two forms of β-(2-hydroxy-3 : 5-dimethylbenzoyl)acrylic acid have been encountered (see Experimental section), namely, a yellow form, m. p. 149—153°, and a red form, m. p. 134—136°, into which the yellow form changed on standing under alcohol. Both gave the same hydrogen bromide adduct. The red form exhibited light absorption which

characterised it as a mixture, probably of *cis*- and *trans*-forms, whilst the yellow, less stable form is probably the *cis*-form (cf. Iskrié, *Arhiv. Kem.*, 1954, **26**, 109; Rice, *J. Amer. Chem. Soc.*, 1923, **45**, 223).



Experimental

Light-absorption measurements were performed in alcohol.

2 : 4-*Xylyl Hydrogen Maleate* (II).—2 : 4 : 1-Xylenol (5 g.), suspended in water (40 c.c.) containing sodium carbonate (2·17 g.), was stirred vigorously whilst powdered maleic anhydride (4·02 g.) was slowly added. When addition was complete, the solution was acidified, and the liberated yellow oil was extracted with benzene, from which the ester was leached with several portions of sodium carbonate solution. The combined extracts were slowly added to a well-stirred mixture of crushed ice and hydrochloric acid, and the precipitated *ester* (3·2 g.; m. p. 40—45°) crystallised from light petroleum as needles, m. p. 81·5—83° (Found: C, 66·5; H, 6·1. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). It readily dissociated on storage and good analyses could not be obtained. Reduction in methyl alcohol over palladised charcoal gave 2 : 4-xylyl hydrogen succinate (Cocker, Fateen, and Lipman, *J.*, 1951, 929).

2 : 4-*Xylyl Hydrogen Fumarate*.—Bromosuccinic anhydride (22 g.) was heated at 145° for 4 hr. with 2 : 4 : 1-xylenol (12 g.). The mixture was then rapidly chilled to 0° and extracted with sodium carbonate solution, and the extract washed with ether. Acidification of the alkaline extract at 0° gave an oil, which on extraction with benzene gave a solid (1·5 g.; m. p. 93—97°) and a gum (8 g.). Two crystallisations of the solid from benzene gave the required *ester* as needles, m. p. 97—98° (Found: C, 65·7; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). Catalytic reduction, slower than in the case of its isomer, gave 2 : 4-xylyl hydrogen succinate, whilst attempted rearrangement with aluminium chloride gave fumaric acid. 2 : 4-Xylyl hydrogen maleate, in the ultra-violet range above 2150 Å, showed only a small inflexion at 2620 Å (log ε 3·07), whilst its *trans*-isomer showed a more pronounced inflexion, or maximum, at 2650 Å (log ε 3·22). These figures correspond closely to those quoted by Ley and Wingchen (*Ber.*, 1934, **67**, 501) for maleic and fumaric acid respectively.

Rearrangement of 2 : 4-*Xylyl Hydrogen Maleate*. 4-*Hydroxy*-5 : 7-*dimethyl*-3-*oxoindane*-1-*carboxylic Acid* (III).—The ester (2 g.) was powdered with aluminium chloride (6 g.), and the mixture was heated at 140—150° for 40 min. and added to ice and hydrochloric acid. The gum so produced was rubbed with benzene–light petroleum, giving a solid (0·2 g.; m. p. 130—150°) which after several crystallisations from benzene followed by dilute methyl alcohol gave the *acid* (III) as buff prisms, m. p. 170—171°, which gave an intense blue ferric reaction, $\lambda_{max.}$ 2170, 2650, 3350 Å (log ε 4·31, 4·12, and 3·76 respectively) (Found: C, 66·1; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). Its *semicarbazone* consisted of pale yellow needles (from dilute acetic acid), m. p. 294° (decomp.) (Found: C, 56·2; H, 5·5. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4%). Its *carbanilate* had m. p. 252—254° (decomp.) (Found: C, 72·3; H, 5·8. $C_{25}H_{22}O_4N_2$ requires C, 72·5; H, 5·3%). Its *methyl ester*, prepared from the acid and methanolic hydrogen chloride, consisted of needles (from dilute methyl alcohol), m. p. 63—64° (Found: C, 67·0; H, 6·0. $C_{13}H_{14}O_4$ requires C, 66·7; H, 5·9%). Reduction of the acid by the Clemmensen method gave 4-*hydroxy*-5 : 7-*dimethylindane*-1-*carboxylic acid* as buff prisms (from benzene)

m. p. 180—181° (Found : C, 70·6; H, 6·9; equiv., 192. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%; equiv., 206).

6 : 8-*Dimethyl-4-oxochroman-2-carboxylic Acid* (IV).—A boiling solution of 2 : 4-xylyl hydrogen maleate (3 g.) in tetrachloroethane (40 c.c.) was treated during 30 min. with finely powdered aluminium chloride (22·8 g.). Further solvent (40 c.c.) was then added and the mixture was boiled for 40 min., cooled, poured into ice and hydrochloric acid, and set aside overnight. The aqueous layer was extracted with ether, and the combined organic extracts were distilled in steam, giving recovered xylenol (11 g.), and a gum (15 g.) from which the aqueous liquor was decanted. The gum on extraction with sodium carbonate, filtration of the extract, and acidification gave the acid (III) (1·1 g.) obtained by the first method. The aqueous liquors, on cooling, deposited a solid (1·5 g.), m. p. 155—170°, which on crystallisation from dilute alcohol afforded 6 : 8-*dimethyl-4-oxochroman-2-carboxylic acid* (IV) as colourless needles, m. p. 170°, depressed to 140—150° by the acid (III). It failed to give a ferric reaction (Found : C, 66·2; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

β-(2-*Hydroxy*-3 : 5-*dimethylbenzoyl*)*acrylic acid* was prepared by the method of Baddeley *et al.* (*loc. cit.*). After decomposition of the aluminium chloride complex with ice and hydrochloric acid, the solvent was removed by distillation in steam, giving the acrylic acid (43%) as red needles, m p. 134—136° (Dr. Baddeley; personal communication), $\lambda_{max.}$ 2250, 2640, 2740, 2920, 3860 Å (log ε 4·22, 4·01, 4·04, 4·05, and 3·51 respectively). Its *methyl ester*, prepared by methyl alcohol and sulphuric acid, consisted of bronze needles (from methyl alcohol), m. p. 97—98°, $\lambda_{max.}$ 2170, 2590, 3410 Å (log ε 4·41, 4·02, and 3·67 respectively) (Found : C, 66·6; H, 5·9. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). When the steam-distillation was protracted, a bronze-coloured viscous mass was obtained.

When the product after decomposition of the aluminium chloride complex was shaken for a few minutes, the gum rapidly solidified, giving a yellow *form* of the acrylic acid (73% yield) as flat needles (from dilute methyl alcohol), m. p. 149—153°, $\lambda_{max.}$ 2650, 3530 Å (log ε 3·98, and 3·53 respectively) (Found : C, 64·9; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). Addition of hydrogen bromide in acetic acid to either the yellow or the red form gave α-*bromo*-β-(2-*hydroxy*-3 : 5-*dimethylbenzoyl*)*propionic acid* (cf. Clemo, Haworth, and Walton, *J.*, 1929, 2368; Cocker and Lipman, *J.*, 1947, 533; Cocker, Lipman, and Whyte, *J.*, 1950, 1519) as yellow plates (from benzene), m. p. 147—148° (decomp.) $\lambda_{max.}$ 2170, 2600, 3490 Å (log ε 4·26, 4·02, and 3·67 respectively) (Found : C, 47·8; H, 4·3. $C_{12}H_{13}O_4Br$ requires C, 47·8; H, 4·3%).

Experiments using Tripropylamine and (I).—(*a*) Methyl β-(2-hydroxy-3 : 5-dimethylbenzoyl)-acrylate (2·3 g.) was dissolved in absolute alcohol (50 c.c.) containing diethyl malonate (8 g.), and tripropylamine (0·4 c.c.) was added. The solution was kept at 0° overnight, and then cooled to −10°; a solid (1·2 g.) was deposited. It was collected and crystallised from alcohol, to give *methyl* 6 : 8-*dimethyl-4-oxochroman-2-carboxylate* as needles, m. p. 98—100°, $\lambda_{max.}$ 2170, 2590, 3410 Å (log ε 4·45, 4·05, and 3·69 respectively) (Found : C, 66·8; H, 6·3. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The corresponding acid, obtained when the ester was refluxed with a mixture of concentrated hydrochloric acid and acetic acid, gave m. p. 168—170°, undepressed by the oxochroman obtained in the Fries rearrangement described above.

(*b*) When the acrylic ester (1·1 g.) in alcohol (12 c.c.) and tripropylamine (0·2 c.c.), but without malonic ester, were used, crystallisation took place in 30 min. but the mixture was set aside for 2 days. The product [*?methyl* 3 : 4-*di*-(2-*hydroxy*-3 : 5-*dimethylbenzoyl*)*hex*-3-*enedioate* (VIII)] (0·4 g.) crystallised from alcohol as yellow needles, m. p. 143—144°, $\lambda_{max.}$ 2180, 2610, and 3440 Å (log ε 4·72, 4·42, and 3·94 respectively) [Found : C, 66·6; H, 6·3; active H, 0·48%; *M* (Rast), 405. $C_{24}H_{28}O_8$ requires C, 66·7; H, 6·0; active H, 0·43%; *M*, 468]. When the acrylic ester (2·3 g.) in alcohol (24 c.c.) was treated with malonic ester (2 g.) and tripropylamine (0·4 c.c.), the yellow dimer (VIII) (1·1 g.) and the oxochroman ester (0·2 g.) were both produced.

Diethyl 2 : 4-*Dimethylphenoxyfumarate*.—This *ester* was obtained by the method of Baddeley *et al.* (*loc. cit.*) as a yellow liquid, b. p. 180°/8 mm. (Found : C, 65·75; H, 7·0. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·8%). The corresponding *acid* (VI) consisted of needles, m. p. 216° (from dilute methyl alcohol) (Found : C, 61·2; H, 5·3%; equiv., 118. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%; equiv., 118). Its *amide* (needles from alcohol) had m. p. 226° (Found : C, 61·4; H, 5·9. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%).

Reduction of the ester over Adams's catalyst gave a liquid, b. p. 220°/43 mm., with a strong terpene-like odour, which on hydrolysis gave 2 : 4-*dimethyl*cyclo*hexyloxysuccinic acid* as tablets, m. p. 156—157° (Found : C, 58·8; H, 8·1. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2%).

α-2 : 4-*Dimethylphenoxy-γ-butyrolactone* (VII; R = R′ = Me).—α-Bromo-γ-butyrolactone and the sodium salt of 2 : 4 : 1-xylenol were condensed according to Julia's method (*loc. cit.*),

giving (VII) (64%), b. p. 224—226°/6 mm., which solidified and was crystallised as colourless plates (from light petroleum), m. p. 62—63° (Found: C, 70·25; H, 6·9. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%).

Oxidation of the Lactone (VII; R = R′ = Me).—The lactone (6·1 g.) was heated with potassium hydroxide (1·88 g.) in water (50 c.c.) for ½ hr. The solution, just alkaline to litmus, was cooled to 5° and sodium carbonate (1·06 g.) was added. Potassium permanganate (9·48 g.) in water (185 c.c.) was added dropwise with stirring during 20 min. at ⩾ 10°. Stirring was continued for a further 3 hr. and the mixture was then set aside for 2 days. Manganese dioxide was collected, and the filtrate was concentrated to half its original bulk and then acidified with 25% hydrochloric acid. The colourless oil obtained was extracted several times with ether and with chloroform, giving the unorientated acid (IX; R = Me; R′ = CO_2H or *vice versa*) (1·05 g.), m. p. 129—130°, which crystallised from benzene–alcohol as colourless rhombs, m. p. 135—136°, $\lambda_{max.}$ 2570 Å (log ε 4·18) (Found: C, 57·0; H, 5·3%; equiv., 131·5. Calc. for $C_{12}H_{14}O_6$: C, 56·7; H, 5·5%; equiv., 127). The corresponding butyrolactone (VII) was obtained as plates (from dilute alcohol), m. p. 170°, $\lambda_{max.}$ 2520 Å (log ε 4·12) (Found: C, 60·8; H, 5·2%; equiv., 116. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%; equiv., 119).

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The Constituents of Natural Phenolic Resins. Part XXIII. The Constitution of Sesamolin.*

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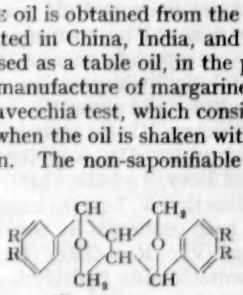
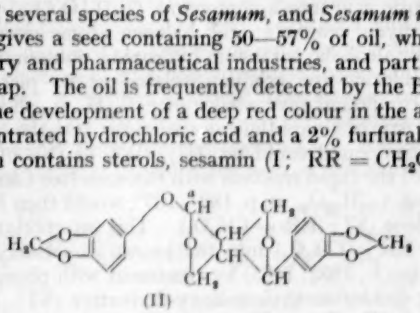
The structure (II), proposed by Boeseken and Cohen (*Rec. Trav. chim.*, 1936, **55**, 815), for sesamolin has been substantiated by degradation of the natural product to the naphthalenes (III) and (VI; RR = CH_2O_2), and the nitro-lactone (VIII; RR = CH_2O_2). Structures (VI; RR = CH_2O_2) and (VIII; RR = CH_2O_2) were established by conversion of the substances into the corresponding dimethoxy-derivatives (VI; R = OMe), identical with pyroguaiacin methyl ether, and (VIII; R = OMe), identical with the compound obtained by the action of concentrated nitric acid on bromonitropinoresinol dimethyl ether (XI; R = OMe). The compound (VIII; RR = CH_2O_2) was also prepared from bromonitrosesamin (XI; RR = CH_2O_2) by the action of concentrated nitric acid.

SESAME oil is obtained from the seeds of several species of *Sesamum*, and *Sesamum indicum* cultivated in China, India, and Japan gives a seed containing 50—57% of oil, which has been used as a table oil, in the perfumery and pharmaceutical industries, and particularly in the manufacture of margarine and soap. The oil is frequently detected by the Badouin or Villavecchia test, which consists of the development of a deep red colour in the aqueous phase when the oil is shaken with concentrated hydrochloric acid and a 2% furfuraldehyde solution. The non-saponifiable fraction contains sterols, sesamin (I; RR = CH_2O_2) and



(I)



(II)

sesamolin, the last having been shown to be responsible for the Badouin reaction. Whilst the lignan structure (I) is well established for sesamin (Bruchhausen and Gerhard, *Ber.*, 1939, **72**, 830), much of the chemistry of sesamolin is discussed in inaccessible papers and its constitution remains unsettled. Villavecchia and Fabris (*Z. angew. Chem.*, 1893, **17**,

* Part XXII, *J.*, 1950, 71.

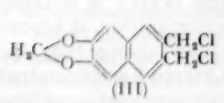
505), Bomer (*Z. Untersuch. Nahr. u. Genussm.*, 1899, **2**, 705), and Heiduschka (*Chem. Ztg.*, 1912, **36**, 1272) were unable to isolate sesamolin in a crystalline state. Kreis (*Chem. Ztg.*, 1903, **27**, 1030) showed that the compound responsible for the Badouin test was phenolic and although he was unable to purify the substance he called it sesamol. Canzoneri and Perciabosco (*Gazzetta*, 1903, **33**, II, 253) obtained a crystalline substance, m. p. 92°, which Adriani (*Z. Lebensm.-Untersuch.*, 1928, **58**, 157) later named sesamolin. Malagnini and Armanni (*Rend. Soc. chim. ital.*, 1907, **5**, 133), isolated both sesamolin and sesamol in crystalline forms, and showed that the latter was 4 hydroxycatechol methylene ether. Adriani (*loc. cit.*) showed sesamolin to have a molecular formula of $C_{20}H_{18}O_7$ and $[\alpha]_D$ +218°, confirmed the formation of sesamol, and showed that a neutral compound, samin, $C_{13}H_{14}O_5$, m. p. 106°, $[\alpha]_D$ +103°, was also produced during the hydrolysis of sesamolin. The constitution of sesamol is well established by three syntheses (Malagnini and Armanni, *loc. cit.*; Boeseken and Cohen, *Rec. Trav. chim.*, 1936, **55**, 815—820; Takata and Matsuda, *J. Pharm. Soc. Japan*, 1954, **74**, 693—694). Boeseken and Cohen also prepared the β-glucoside of sesamol, which, like sesamolin, slowly gave the red colour in the Badouin test, as distinct from sesamol which gave an immediate reaction. Boeseken and Cohen (*loc. cit.*) concluded that sesamolin was a type of glucoside of sesamol and suggested a structure (II), presumably on the basis of a hypothetical relation with sesamin (I; RR = CH_2O_2). This structure (II) contains two points of outstanding interest which encouraged a further investigation of the problem. It represents the first occurrence of a 4-hydroxycatechol methylene ether derivative in natural products and, secondly, it represents a unique variant of the lignan skeleton, which in all other cases is derived by union of two C_6C_3 units at the middle carbon atom in the C_3 system.

Two new methods were developed for the isolation of sesamolin from sesame oil, both depending in the first place on the removal of sesamin and sesamolin from the large quantities of glycerides in the oil. This was achieved either by adsorption of the aromatic constituents on a column of alumina, or by cooling to −50° an acetone solution of the oil, whereupon the glycerides separated; the latter method has also been developed during the course of our work by Budowski (*J. Amer. Oil Chemists' Soc.*, 1950, **27**, 164). The sesamin–sesamolin mixture was then separated by fractional crystallisation, and sesamin and sesamolin were obtained in yields of 0·6 and 0·15% respectively from sesame oil.

Our first approach aimed at a repetition of Adriani's hydrolysis of sesamolin to sesamol and samin and then structural investigation of the latter product. Although no difficulty was experienced in the isolation of the phenol sesamol, many attempts, using a wide variety of conditions, to obtain the neutral component, samin, in a crystalline form were unsuccessful. Hydrolysis of sesamolin with concentrated hydrochloric acid in ether–ethanol gave sesamol, and a pale yellow oil which was converted by further treatment with hydrochloric acid into a compound, $C_{13}H_{10}O_2Cl_2$. This dichloro-compound did not react with aldehydic reagents; the halogen atoms were readily removed by treatment with aqueous or alcoholic potassium hydroxide, potassium cyanide, or especially thiourea, which gave a chlorine-free product isolated as its picrate. Catalytic hydrogenation of the dichloro-compound gave a substance, $C_{13}H_{12}O_2$, showing an ultra-violet absorption spectra characteristic of a naphthalene structure. On the basis of structure (II) for sesamolin, the dichloro-compound could be (III), (IV), or (V), of which structure (III) is preferred on account of the rapid reaction with thiourea (see Campbell and Levy, *J.*, 1939, 1442). The compound, $C_{13}H_{12}O_2$, m. p. 186—187°, would then be 2 : 3-dimethyl-6 : 7-methylenedioxynaphthalene (VI; RR = CH_2O_2). This interpretation has been confirmed by conversion of (VI; RR = CH_2O_2) into the known dimethoxy-analogue (VI; R = OMe) (Haworth and Mavin, *J.*, 1932, 1485) by treatment with phosphorus pentachloride, hydrolysis of the resulting dichloromethylenedioxy-derivative (VI; RR = CCl_2O_2) to the 6 : 7-dihydroxy-compound (VI; R = OH), and finally methylation.

Whilst these observations are consistent with formula (II; RR = CH_2O_2) for sesamolin, they by no means establish it, and further interesting results have been obtained from a study of the action of bromine on sesamolin. Bromosesamol (5-bromo-4-hydroxycatechol methylene ether) was readily identified, and a crystalline neutral component, $C_{26}H_{26}O_9$, was also isolated. Attempted dehydration of the latter, dehydrogenation, mild

oxidation, and catalytic reduction were unsuccessful, hydrochloric or sulphuric acid in acetic acid did not affect it, and the infra-red and chemical examinations suggested that all the oxygen atoms were ethereal. On the basis of (II), structure (VII) is suggested for the substance $C_{26}H_{26}O_9$. As this compound is also obtained, with sesamol, when concentrated hydrochloric acid is added to an ice-cooled solution of sesamolin in ether or acetic acid, it is probable that its formation by the action of bromine is due to the liberation of hydrogen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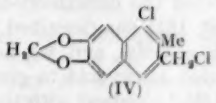
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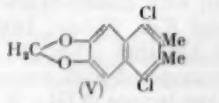
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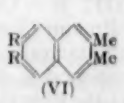
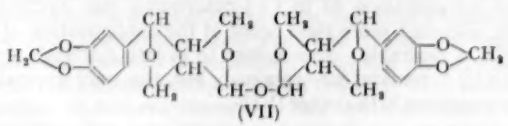

(VI)

bromide during the production of bromosesamol. When this ether (VII) was treated with nitric acid it was converted into a nitro-compound, $C_{13}H_{11}O_7N$, containing a lactone group, the presence of which was confirmed both by the action of sodium hydroxide and by infra-red measurements. Structure (VIII; RR = CH_2O_2) assigned to the nitro-compound is derived from the ether (VII) by nuclear nitration, hydrolysis of the ether linkage, and subsequent oxidation to the γ-lactone. In agreement with this view the ether (VII) is readily hydrolysed and converted into the bischloromethylnaphthalene (III) by warm hydrochloric acid; a similar cyclisation, however, was not realisable in the case of the nitro-compound.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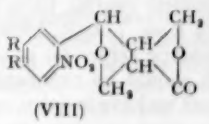
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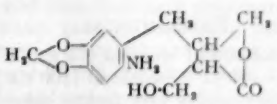
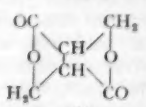
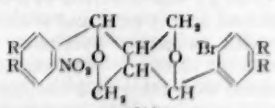

(IX)

The nitro-lactone (VIII; RR = CH_2O_2) was reduced by hydrogen in the presence of palladium–charcoal to an amine (IX), which gave a crystalline *N*-acetyl compound and a well defined Schiff's base with *p*-nitrobenzaldehyde. The analyses of these derivatives indicated that the benzyl ether linkage has also been reduced, as would be expected, and the presence of a hydroxyl group was supported by the infra-red spectrum of the Schiff's base.

Attempts to prepare the un-nitrated parent of (VIII; RR = CH_2O_2) were unsuccessful because of the ease of nitration of the ether (VII) which took place with dilute (0·5N) nitric acid. The nitro-lactone was not attacked by concentrated nitric acid but a small yield of 4 : 5-dinitromethylenedioxybenzene was obtained on treatment with fuming nitric acid, although we were unable to isolate the dilactone of 2 : 3-bishydroxymethylsuccinic acid (X) which Erdtmann (*Acta Chem. Scand.*, 1947, **1**, 71) had prepared from dibromopinoresinol dimethyl ether (XI; R = OMe; Br for NO_2) by the action of concentrated nitric acid and which we have prepared in a similar manner from dibromosesamin (XI; RR = CH_2O_2; Br for NO_2) and also in small yield by the action of fuming nitric acid on sesamin. In view


(X)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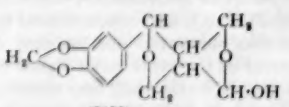
(XII)

of these experiments it appeared feasible that, if bromonitrosesamin (XI; RR = CH_2O_2) could be prepared, degradation with concentrated nitric acid should lead to (VIII; RR = CH_2O_2) and thus provide confirmatory evidence of the structure assigned to the nitration product of sesamolin. Early attempts to prepare bromonitrosesamin were unsuccessful but fortunately an alternative but similar approach was made possible by the ready

conversion of the nitro-compound (VIII; RR = CH_2O_2) into the dimethoxy-analogue (VIII; R = OMe). It was shown that 4-nitrocatechol methylene ether, 4 : 5-dinitrocatechol methylene ether, and the nitrated lactone (VIII; RR = CH_2O_2) were readily hydrolysed by warm aqueous sodium hydroxide to the corresponding catechols, although dinitrosesamin was unaffected under similar conditions (possibly owing to its relative insolubility in an aqueous medium). Methylation of the phenolic hydrolysis product (VIII; R = OH) with diazomethane yielded the dimethoxy-lactone (VIII; R = OMe). Erdtmann (*Svensk Kem. Tidskr.*, 1938, **50**, 161) has described the preparation of bromonitropinoresinol dimethyl ether (XI; R = OMe) and we have now shown that this compound is decomposed with concentrated nitric acid to give 4-bromo-5-nitroveratrole and the dimethoxy-lactone (VIII; R = OMe) identical with the compound obtained from sesamolin.

When these experiments had been completed it was found possible to prepare nitrosesamin and thence bromonitrosesamin (XI; RR = CH_2O_2); degradation of the latter with concentrated nitric acid at 50° gave 4-bromo-1 : 2-methylenedioxy-5-nitrobenzene and the nitro-lactone (VIII; RR = CH_2O_2).

From these experiments it can be deduced that in sesamolin the sesamol is united to the carbon atom represented by the carbonyl group in the nitrated lactone (VIII; RR = CH_2O_2). Welcome confirmation of formula (II), suggested by Boeseken and Cohen (*loc. cit.*), has consequently been obtained and it may also be concluded that in sesamolin the asymmetric centres have the same configuration as in (+)-pinoresinol (see Erdtmann, *Svensk Kem. Tidskr.*, 1936, **48**, 230), although more rigid proof of the configuration of the asymmetric centre (*a*) in formula (II) is desirable. Our failure to isolate Adriani's samin which should be represented by (XII) * remains unexplained, but the only crystalline product we have isolated from these reactions is the ether (VII).

Experimental

Isolation of Sesamolin.—(*a*) A column of alumina (75 g.; 4″ in length, 1½″ diameter) was set up in light petroleum (b. p. 60—80°). Sesame oil (100 c.c.) was passed down the column (1 day), and the fat was removed by washing with further solvent until the eluate gave a slight Badouin test. The portion immediately below the strong yellow band in the column was removed, and continuously extracted with ether (Soxhlet) for 6 hr. Removal of the solvent gave a yellow oil, which was saponified with 5% alcoholic potassium hydroxide (25 c.c.) for 1 hr. Water (100 c.c.) was added and the soap solution thrice extracted with ether (60 c.c.). Removal of the ether gave a yellow resin (approx. 2 g.) which was dissolved in ether (10 c.c.) and overnight yielded crystals of sesamin (0·5 g.). The filtrate, after removal of the ether, was dissolved in chloroform (1 c.c.), and light petroleum (b. p. 90—120°) was added until the onset of cloudiness. Sesamolin separated as a white solid which crystallised from ethanol in white plates (0·10—0·15 g.), m. p. 93—94°.

(*b*) Sesame oil (200 c.c.) was dissolved in acetone (1500 c.c.) and cooled overnight in acetone and solid carbon dioxide. The glyceride crystals were separated by filtration and removal of the acetone from the filtrate gave a yellow oil which was saponified and separated into its constituents as in (*a*). The sesamolin (0·3—0·35 g.) had m. p. 93—94° (Found: C, 64·7, 65·0; H, 4·8, 4·8. Calc. for $C_{20}H_{18}O_7$: C, 64·9; H, 4·9%).

Zerewitinoff determinations showed no active hydrogen to be present in sesamolin. Infrared analysis of sesamin and sesamolin showed no hydroxyl or carbonyl band.

Hydrolysis of Sesamolin.—Sesamolin (0·25 g.) was dissolved in a mixture of ether (15 c.c.), ethanol (2 c.c.), and concentrated hydrochloric acid (5 c.c.), and shaken for ½ hr. The ethereal layer was separated and washed twice with 2N-sodium hydroxide (5 c.c.) and with water. Removal of the ether gave a pale yellow oil (A) (0·15 g.). The alkaline extracts were acidified with 2N-sulphuric acid, and sesamol, isolated with ether and distilled at 70° (bath)/0·01 mm., was obtained in fine white needles (0·02 g.), m. p. 59—61°, giving an immediate Badouin test and a violet colour with ferric chloride. Recrystallisation from chloroform–light petroleum (b. p. 40—60°) raised the m. p. to 62—63°, and the product gave no depression on admixture with a synthetic specimen of sesamol (Boeseken and Cohen, *loc. cit.*). The *toluene-p-sulphonate* crystallised from methanol in needles, m. p. 86—87° (Found: C, 57·4; H, 3·9. $C_{14}H_{12}O_5S$

* After discussion with the Editor, it is proposed to refer to structures (XII) and (VII) as samino and disaminyl ether respectively.

requires C, 57·5; H, 4·1%). The oil (A) (0·15 g.) was heated on a water bath at 60—70° for ½ hr. with concentrated hydrochloric acid (5 c.c.). The light yellow solid which gradually separated was extracted with ether and purified by filtration in benzene (5 c.c.) through alumina. Recovery gave a white solid which crystallised from ethanol in needles, m. p. 146—147° (Found: C, 57·5, 58·3; H, 3·7, 4·0. $C_{13}H_{10}O_3Cl_2$ requires C, 58·0; H, 3·7%). 2 : 3-*Bischloromethyl*-6 : 7-*methylenedioxynaphthalene* (III) did not form a picrate and its ultra-violet absorption curve possessed no characteristic maxima, although its general shape conformed to that expected from a naphthalene derivative.

After the substance (III) had been boiled with thiourea (0·1 g.) in ethanol (3 c.c.) for 10 min., picric acid (0·1 g.) was added and the mixture heated until dissolution was complete. On cooling, a yellow crystalline *picrate* separated, which crystallised from ethanol in yellow needles (0·15 g.), m. p. 236—237° (Found: C, 40·4; H, 2·9; S, 8·6. $C_{27}H_{22}O_{16}N_{10}S_2$ requires C, 40·2; H, 2·8; S, 8·0%).

2 : 3-*Dimethyl*-6 : 7-*methylenedioxynaphthalene* (VI; RR = CH_2O_2).—Substance (III) (0·10 g.) was hydrogenated in glacial acetic acid (10 c.c.) with 15% palladium–charcoal (0·015 g.) for 2 hr. (uptake of H_2, 18·5 c.c.). Removal of the solvent gave 2 : 3-*dimethyl*-6 : 7-*methylenedioxynaphthalene* (VI; RR = CH_2O_2) which crystallised from ethanol in white plates (0·06 g.), m. p. 186—187° (Found: C, 77·7; H, 5·9. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%). Ultra-violet absorption in EtOH: max. at 2650, 2780, and 2885 Å (log ε 3·71, 2·69, 3·52), min. at 2975 Å (log ε 3·05). The picrate, m. p. 162—163°, decomposed on crystallisation from alcohol.

2 : 3-*Dimethyl*-6 : 7-*dimethoxynaphthalene* (VI; R = OMe).—A solution of phosphorus pentachloride (0·2 g.) in benzene (2 c.c.) was added to the substance (VI; RR = CH_2O_2) (0·1 g.) dissolved in five drops of dry benzene, and after 3 hours' refluxing the mixture was decomposed with ice. The benzene layer was dried ($CaCl_2$) and removal of the solvent gave a blue solid which was dissolved in methanol (2 c.c.) and methylated during 2 hr. with sodium hydroxide (20%; 1·5 c.c.) and methyl sulphate (0·6 c.c.). The product, isolated with ether and purified by filtration in benzene through a very short column of alumina, was a colourless oil which crystallised first from ethanol and then from light petroleum (b. p. 60—80°) in colourless plates (0·015 g.), m. p. 149—150°, which gave no depression with a synthetic specimen of 6 : 7-dimethoxy-2 : 3-dimethylnaphthalene (Haworth and Mavin, *loc. cit.*). Ultra-violet absorption in ethanol: max. at 2580, 2685, and 2750 Å (log ε 3·67, 3·68, 3·62) and min. at 3000 Å (log ε 3·07). The picrate was prepared in ethanol and crystallised from the same solvent in red needles, m. p. 132—133° (Found: C, 53·9; H, 4·6; N, 9·0. Calc. for $C_{20}H_{19}O_9N_3$: C, 53·9; H, 4·3; N, 9·4%).

Action of Bromine on Sesamolin.—A 20% solution of bromine in glacial acetic acid (0·5 c.c.) was added with stirring to an ice-cooled solution of sesamolin (0·25 g.) in glacial acetic acid (0·8 c.c.). After 10 min., the solution was diluted with chloroform (10 c.c.) and ether (20 c.c.) and washed twice with 2N-sodium hydroxide (10 c.c.) (B) and then water. Removal of the solvents gave *disaminyl ether* (VII), which crystallised from ethanol in plates (0·07 g.), m. p. 191—192°, $[\alpha]_D$ +143° (*c* 1·74 in $CHCl_3$) [Found: *M*, 466 (Rast), 481 (cryoscopic in benzene); C, 64·9, 64·7, 64·7; H, 5·6, 5·7, 5·4. $C_{34}H_{26}O_9$ requires *M*, 482; C, 64·8; H, 5·4%). Ultra-violet absorption in EtOH: max. at 2865 and 2355 Å (log ε 3·90, 3·94) and min. at 2555 Å (log ε 2·99). Zerewitinoff determinations did not show the presence of active hydrogen in the compound. The alkaline washings (B above) gave on acidification (2N-sulphuric acid) a brown oil, which after extraction with ether was sublimed at 80° (bath)/0·01 mm.; *bromosesamol* was obtained as white needles (0·03 g.), m. p. 82—83° (Found: C, 38·6; H, 2·4. $C_7H_5O_3Br$ requires C, 38·8; H, 2·3%), identical with the compound prepared by bromination of sesamol in acetic acid solution.

Action of Hydrochloric Acid on Sesamolin.—Concentrated hydrochloric acid (3 drops) was added to an ice-cooled solution of sesamolin (0·1 g.) in glacial acetic acid (5 c.c.). After 10 min. dilution and extraction with chloroform–ether, followed by washing with 2N-sodium hydroxide (the washings gave sesamol on acidification), yielded disaminyl ether (VII) (0·03 g.).

Hydrolysis of Disaminyl Ether (VII).—A mixture of disaminyl ether (VII) (0·04 g.), glacial acetic acid (1 c.c.), and concentrated hydrochloric acid (5 c.c.) was warmed at 60—70° for 10 min. and the pale yellow solid, which was precipitated, collected and purified by filtration in benzene (5 c.c.) through a layer of alumina. Removal of the solvent gave a solid which crystallised from alcohol in needles (0·02 g.), m. p. 146—147°, undepressed on admixture with a specimen of (III).

Action of Nitric Acid on Disaminyl Ether (VII).—Disaminyl ether (VII) (0·04 g.) was dissolved in glacial acetic acid (0·5 c.c.), and concentrated nitric acid (1·0 c.c.) added. After 1½ hr. at

30—40°, the mixture was diluted with water (15·0 c.c.) and the solid (0·035 g.) collected and crystallised from ethanol, giving yellow needles (0·030 g.), m. p. 154—155°, $[\alpha]_D$ −9·7° (*c* 3·39 in $CHCl_3$) (Found: C, 53·2, 53·4; H, 3·8, 4·0; N, 4·5. $C_{13}H_{11}O_7N$ requires C, 53·3; H, 3·8; N, 4·8%). This *tetrahydro-2-hydroxymethyl-*1-(3 : 4-*methylenedioxy-5-nitrophenyl*)*furan-3-carboxylic lactone* (VIII; RR = CH_2O_2) was insoluble in sodium hydrogen carbonate solution but gave a deep red solution in warm 2N-sodium hydroxide. Ultra-violet absorption in EtOH: max. at 2460 and 2950 Å (log ε 4·07, 3·50) and min. at 2700 Å (log ε 3·25). Infra-red analysis of the compound in a Nujol mull showed a strong band at 1782 cm.$^{-1}$ indicative of a γ-lactone.

Action of 2N-*Sodium Hydroxide on* 4-*Nitrocatechol Methylene Ether.*—This ether (1·0 g.) was warmed with 2N-sodium hydroxide (10 c.c.) on a water-bath. A blood-red solution was formed, which was extracted with ether after 30 min. to remove unchanged starting material, acidified, and extracted with ether to yield 4-nitrocatechol, which crystallised from water in pale yellow needles (0·6 g.), m. p. 175—176° (Kempf, *J. pr. Chem.*, 1908, **78**, 257, gives 175·5°). The *dibenzoate* crystallised from ethanol in white needles, m. p. 157—158° (Found: C, 65·9; H, 3·4. Calc. for $C_{20}H_{13}O_6N$: C, 66·1; H, 3·6%).

Action of 2N-*Sodium Hydroxide on* (VIII; RR = CH_2O_2) *and Methylation of the Product.*—A mixture of the compound (VIII; RR = CH_2O_2) (0·05 g.) and 2N-sodium hydroxide (5 c.c.) was heated on a steam-bath for ½ hr. After extraction with ether to remove unchanged material, the deep red solution was acidified with 2N-sulphuric acid and thrice extracted with ether to give a pale yellow solid, which gave a blue ferric chloride test. This phenol (VIII; R = OH) was dissolved in ether (5 c.c.), and an excess of ethereal diazomethane solution added. After 2 hr., the solvent was removed and 1-(3 : 4-*dimethoxy-5-nitrophenyl*)*tetrahydro-2-hydroxymethyl-furan-3-carboxylic lactone* (VIII; R = OMe) separated from ethanol in pale yellow clusters (0·02 g.), m. p. 157—158°, $[\alpha]_D$ −67·7° (*c* 3·4 in $CHCl_3$) (Found: C, 54·4; H, 4·4. $C_{14}H_{15}O_7N$ requires C, 54·4; H, 4·9%). Ultra-violet absorption in EtOH: max. at 2440 and 3020 Å (log ε 3·98, 3·62) and min. at 2665 Å (log ε 3·08).

Reduction of the Compound (VIII; RR = CH_2O_2).—The nitro-compound (VIII; RR = CH_2O_2) (0·04 g.) was hydrogenated in glacial acetic acid (5 c.c.) in the presence of 15% palladium–charcoal (0·02 g.). Hydrogen uptake (11·0 c.c. Calc.: 12·3 c.c.) was complete in 2 hr. The catalyst and solvent were removed and the residual brown oil 2-(5-amino-3 : 4-methylenedioxybenzyl)-1-hydroxymethylbutyrolactone (IX), which was easily oxidised in air, gave with acetic anhydride (0·1 c.c.) the N-*acetyl derivative*, which crystallised from ethanol in fine white needles, m. p. 222—223° (Found: C, 58·9, 58·8; H, 5·9, 5·7. $C_{15}H_{17}O_6N$ requires C, 58·7; H, 5·7%). The *N*-acetyl derivative was soluble in warm 2N-sodium hydroxide and was recovered after prolonged boiling with alkali. The p-*nitrobenzylidene derivative*, prepared from the crude amine (IX) in acetic acid, crystallised from the same solvent in orange needles, m. p. 219—220° (Found: C, 48·5; H, 3·4. $C_{20}H_{18}O_7N_2$ requires C, 48·2; H, 3·2%). Infra-red analysis of this compound on a potassium bromide disc showed bands at 1770 (γ-lactone) and at 2860 and 3382 cm.$^{-1}$ probably indicative of a free hydroxyl group.

Action of Concentrated Nitric Acid on Dibromosesamin.—Dibromosesamin (1·5 g.) was added portionwise to nitric acid (*d* 1·4) (20 c.c.) with efficient mechanical stirring. Brown fumes were evolved and the dibromosesamin gradually passed into solution, after which stirring was continued for a further ½ hr. Addition of water (40 ml.) gave 4-bromo-5-nitromethylenedioxybenzene which crystallised from alcohol in yellow plates, m. p. 89—90°. The filtrate was exactly neutralised with potassium hydrogen carbonate and evaporated to dryness and the residue extracted overnight (Soxhlet) with ether. Removal of the ether gave a brown gum which was dissolved in hot water. Filtration and evaporation gave a residue which when extracted with hot benzene (20 c.c.) gave 2 : 3-bis(hydroxymethylsuccinic) dilactone (X), white plates (from ethanol), m. p. 159—160° (Found: C, 50·7; H, 4·2. Calc. for $C_6H_6O_4$: C, 50·7; H, 4·2%). Erdtmann (*Acta Chem. Scand.*, 1947, **1**, 71) gives m. p. 160°.

Action of Concentrated Nitric Acid on Bromonitropinoresinol Dimethyl Ether (XI; R = OMe).—Bromonitropinoresinol dimethyl ether (0·1 g.) (Erdtmann, *loc. cit.*) was slowly added to nitric acid (*d* 1·4) (2 c.c.) with mechanical stirring. The mixture was warmed slightly, brown fumes being evolved, and after ½ hr., the mixture was diluted with water (20 c.c.) and the products were isolated with chloroform as a yellow gum, which was warmed for ½ hr. with 2N-sodium hydroxide (10 c.c.) and extracted with chloroform. The chloroform extract gave 4-bromo-5-nitroveratrole, m. p. 123°, on crystallisation from ethanol. The alkaline extract was acidified and extracted with chloroform to give a brown oil, which, after two crystallisations from ethanol, yielded pale yellow needles (0·02 g.), m. p. 157—158°, identical with (VIII; R = OMe), obtained as described above.

Nitrosesamin.—A solution of nitric acid (*d* 1·4; 0·5 c.c.) in acetic acid–acetic anhydride (2 : 1; 5 c.c.) was added during ½ hr. to a solution of sesamin (2 g.) in the same solvent (15 c.c.) and the temperature kept at 15—20°. Dilution with water (25 c.c.) gave a yellow gum which crystallised from dioxan–methanol, to give pale yellow needles of ***mononitrosesamin*** (0·8 g.), m. p. 139—140°, $[\alpha]_D$ −70° (*c* 2·6 in $CHCl_3$) (Found: C, 59·8; H, 4·3; N, 3·6. $C_{20}H_{17}O_8N$ requires C, 60·1; H, 4·3; N, 3·5%).

Bromonitrosesamin (XI; RR = CH_2O_2).—Nitrosesamin (0·5 g.) was mixed on a watch-glass with a solution of bromine in chloroform (1 : 10; 8 c.c.). Hydrogen bromide was evolved and as the solvent evaporated *bromonitrosesamin* separated. Crystallisation from dioxan–acetic acid gave lemon-coloured needles (0·5 g.), m. p. 199—200°, $[\alpha]_D$ −37° (*c* 2·7 in $CHCl_3$) (Found: C, 50·5; H, 3·5; N, 2·9. $C_{20}H_{16}O_8NBr$ requires C, 50·2; H, 3·3; N, 2·9%).

Action of Nitric Acid on Bromonitrosesamin (XI; RR = CH_2O_2).—Bromonitrosesamin (0·3 g.) was added portionwise to nitric acid (*d* 1·4; 5 c.c.). Brown fumes were evolved at 50° during ½ hr. and, on cooling, needles of 5-bromo-1 : 2-methylenedioxy-4-nitrobenzene separated. The filtrate gave on dilution with water a yellow solid (0·1 g.) which crystallised from ethanol in yellow needles (0·02 g.), m. p. 153—154°, undepressed on admixture with the nitro-lactone (VIII; RR = CH_2O_2), prepared as described on p. 832.

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 10th*, 1954.]

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*Galloflavin. Part II.**

By JAMES GRIMSHAW, ROBERT D. HAWORTH, and (in part) H. K. PINDRED.

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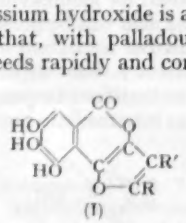
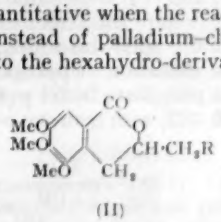
Structure (I; R = CO_2H, R′ = H; or *vice versa*) provisionally suggested for *iso*galloflavin has been confirmed by the oxidation of the hexahydro-decarboxylated derivative (II; R = CH_2·OH) of *iso*galloflavin to a carboxylic acid (II; R = CO_2H) identical with a synthetic specimen.

The mechanism of the formation of galloflavin from gallic acid is also discussed.

IN an earlier paper (Haworth and McLachlan, *J.*, 1952, 1583), *iso*galloflavin, for which structure (I; R = CO_2H, R′ = H; or *vice versa*) was tentatively suggested, has been shown to afford, on methylation and decarboxylation followed by catalytic reduction, tetra- and hexa-hydro-derivatives formulated as (IV) and (II; R = CH_2·OH) respectively. Further studies have now shown that the conversion of galloflavin into *iso*galloflavin by potassium hydroxide is almost quantitative when the reaction is carried out under nitrogen and that, with palladous oxide instead of palladium–charcoal as catalyst, the reduction proceeds rapidly and completely to the hexahydro-derivative (II; R = CH_2·OH).



(I)



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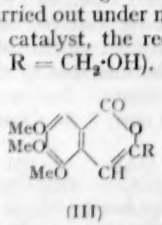


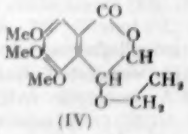
(III)

5 : 6 : 7-Trimethoxy*iso*coumarin-3-carboxylic acid (III; R = CO_2H) has been made readily available by complementary researches (Haworth, Pindred, and Jefferies, *J.*, 1954, 3617) and a synthesis of the hexahydro-derivative (II; R = CH_2·OH) was envisaged starting from this acid. The diazo-ketone (III; R = CO·CHN_2) described by Haworth, Pindred, and Jefferies (*loc. cit.*) readily gives the 3-alkoxyacetyl-5 : 6 : 7-trimethoxy*iso*-coumarin (III; R = CO·CH_2·OEt or CO·CH_2·O·CH_2Ph) on treatment with ethanol or

* Part I, *J.*, 1952, 1583.

benzyl alcohol and a boron trifluoride–ether catalyst according to the general procedure of Newman and Beal (*J. Amer. Chem. Soc.*, 1950, **72**, 5161). The benzyloxyacetyl derivative gave a crystalline ethylene mercaptal; the diethyl mercaptal was an unstable oil. Hydrogenolysis of either with active Raney nickel in boiling alcohol gave a compound, $C_{14}H_{16}O_5$, and not the expected ether (III; R = $CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$). The ultra-violet absorption spectrum of the product was almost identical with that of 4-methyl-5 : 6 : 7-trimethoxy*iso*coumarin (Haworth, Pindred, and Jefferies, *loc. cit.*), suggesting that the compound was 3-ethyl-5 : 6 : 7-trimethoxy*iso*coumarin (III; R = Et), and the *iso*coumarin structure was confirmed by conversion into the corresponding *iso*carbostyril. The expected product (III; R = $CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$), which is a masked β-alkoxy-ketone, may readily lose the elements of alcohol to give the easily reducible αβ-unsaturated ketone (cf. Heilmann, *Bull. Soc. chim.*, 1949, 66).

In view of the failure of this synthesis an attempt was made to oxidise the hexahydro-derivative (II; R = $CH_2{\cdot}OH$) to the corresponding acid (II; R = CO_2H), a synthesis of which was envisaged by ascent from 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (III; R = CO_2H) and subsequent reduction. Oxidation of the hexahydro-derivative (II; R = $CH_2{\cdot}OH$) in dilute acetic acid solution with potassium dichromate and sulphuric acid gave 50% yields of the corresponding acid (III; R = CO_2H) which was obtained in dimorphous modifications, each affording the same methyl ester on methylation with diazomethane. Chain extension of 5 : 6 : 7-trimethoxy*iso*coumarin-3-carboxylic acid (III; R = CO_2H) had previously (*idem*, *loc. cit.*) been effected in poor yield by the classical Wolff rearrangement of the diazo-ketone (III; R = $CO{\cdot}CHN_2$) to give methyl 5 : 6 : 7-trimethoxy*iso*coumarinyl-3-acetate (III; R = $CH_2{\cdot}CO_2Me$), but application of Newman and Beal's conditions (*J. Amer. Chem. Soc.*, 1950, **72**, 5163) gave a marked improvement in yields. Here *tert.*-butanol, with a silver benzoate catalyst in triethylamine solution, gave the *tert.*-butyl ester (III; R = $CH_2{\cdot}CO_2Bu^t$) which on acid hydrolysis afforded an amorphous acid, esterified with diazomethane to give the methyl ester (III; R = $CH_2{\cdot}CO_2Me$) previously reported (Haworth, Pindred, and Jefferies, *loc. cit.*). Catalytic hydrogenation of the *tert.*-butyl ester proceeded smoothly and the oily product on acid hydrolysis gave the diamorphous 3 : 4-dihydro-5 : 6 : 7-trimethoxy*iso*coumarin-3-ylacetic acid (II; R = CO_2H), identical in all respects with the oxidation product of hexahydro-decarboxylated trimethyl*iso*-galloflavin.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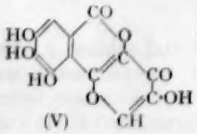
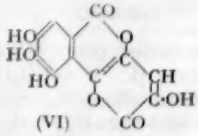
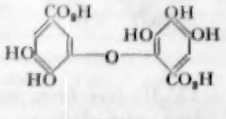
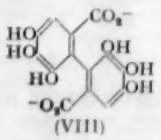
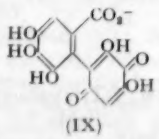

(V)


(VI)

In Part I (*loc. cit.*) formulæ (V) and (VI) were tentatively proposed for galloflavin, and (VI) is now preferred because formation of this structure from gallic acid can be presented by a rational mechanism whereas the open-chain intermediates in the formation of (V) would be unstable to alkali. The oxidation of pyrogallol derivatives is very dependent on conditions. For example, in a phosphate buffer pyrogallol is autoxidised to purpurogallin (Loew, *J. pr. Chem.*, 1877, **15**, 322) with hydroxy-*o*-quinones as intermediate products

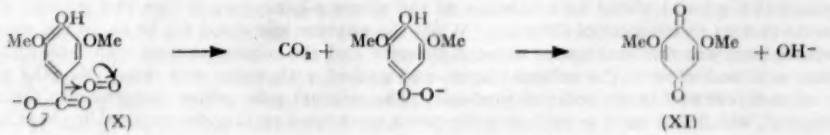

(VII)


(VIII)


(IX)

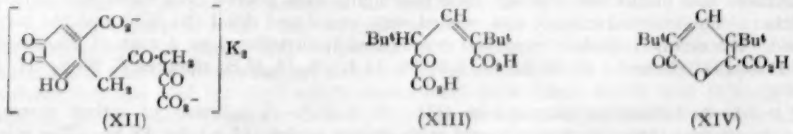
(Critchlow, Haworth, and Pauson, *J.*, 1951, 1319), but in strongly alkaline solution pyrogallol and ethyl gallate yield 2 : 3 : 4 : 2′ : 3′ : 4′-hexahydroxydiphenyl (Harries, *Ber.*, 1902, **35**, 2957) and ellagic acid (Herzig, Tscherne, and Bronneck, *Monatsh.*, 1908, **29**, 277) respectively, presumably by symmetrical dimerisation of semiquinone radicals;

unsymmetrical union of two gallic acid semiquinone radicals will account for the biogenesis of dehydrodigallic acid (VII), isolated by Schmidt and Mayer (*Annalen*, 1952, **578**, 34) from the tannin of Spanish chestnut. When a potassium hydroxide solution of gallic acid is aerated the anion (VIII) is probably produced and converted by further oxidation into (IX), and in support of this stage it has been found that syringic acid (X) is easily oxidised by air to 2 : 6-dimethoxy-*p*-benzoquinone (XI). Structure (IX) may be



(X) (XI)

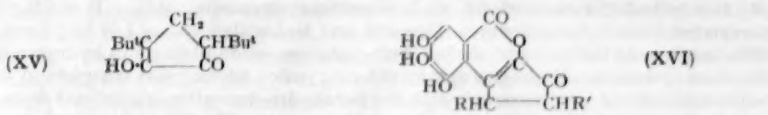
represented in equivalent α- and β-diketone forms and oxidation, hydrolysis, and decarboxylation reactions provide several equally attractive representations of ring rupture leading to the " dipotassium salt " (XII); subsequent conversion of (XII) into galloflavin (VI) presents no difficulty. The " dipotassium salt " precipitated during the preparation



(XII) (XIII) (XIV)

of galloflavin gives an aqueous solution of pH 7—8 and consequently affords carboxylate and not phenoxide ions. It is not a simple salt of galloflavin because whilst the latter may be converted into *iso*galloflavin (I; R = CO_2H, R′ = H) in high yield, the " dipotassium salt " under similar conditions gives an amorphous product which on methylation with diazomethane gives traces only of tetramethyl*iso*galloflavin; the main product is amorphous and insoluble in methanol and contains only 2% of methoxyl.

Support for these views also comes from recent work of Campbell *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 4190) on the oxidation of 4 : 6-di-*tert.*-butylpyrogallol. The products (XIII) and (XIV) arise by reaction mechanisms similar to those proposed above for galloflavin, and the third product (XV) arises by ring contraction of the hydroxy-*o*-quinone intermediate. An analogous change from the galloflavin intermediate ion (VIII) would



(XV) (XVI)

lead to the acid (XVI; R = CO_2H, R′ = H) which, as the vinylogue of a β-keto-acid, may equally well account for the properties of brevifolincarboxylic acid recently isolated from *Algarobilla* by Schmidt and Bernauer (*Annalen*, 1954, **288**, 211) and to which these authors assign structure (XVI; R = H, R′ = CO_2H).

Experimental

3-Ethoxyacetyl-5 : 6 : 7-trimethoxyisocoumarin (III; R = CO·CH_2·OEt).—3-Diazoacetyl-5 : 6 : 7-trimethoxy*iso*coumarin (Haworth, Pindred, and Jefferies, *loc. cit.*) (2 g.) was suspended in ethanol (10 c.c.) and treated with boron trifluoride–ether complex (1 g.). When evolution of nitrogen had ceased, the pale yellow solution was refluxed for 10 min. and cooled; the *α-ethoxyketone* separated and crystallised from ethanol as colourless needles (2 g.), m. p. 122—123° (Found: C, 59·5; H, 5·6. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%). The *2 : 4-dinitrophenylhydrazone* separated from glacial acetic acid in orange needles, m. p. 236—237° (Found: C, 52·9; H, 4·3; N, 11·4. $C_{22}H_{22}O_{10}N_4$ requires C, 52·6; H, 4·4; N, 11·2%).

3-Benzyloxyacetyl-5 : 6 : 7-trimethoxyisocoumarin (III; R = CO·CH_2·O·CH_2Ph).—3-Diazoacetyl-5 : 6 : 7-trimethoxy*iso*coumarin (2 g.) was suspended in benzyl alcohol (6 c.c.) and

treated with boron trifluoride–ether complex (1 g.). When evolution of nitrogen had ceased, the mixture was warmed on a water-bath for 10 min., diluted with an equal volume of methanol, and set aside at 0°. The *α-benzyloxy-ketone* separated and crystallised from a large volume of ethanol as colourless plates (2·2 g.), m. p. 145—146° (Found: C, 65·4; H, 5·3. $C_{21}H_{20}O_7$ requires C, 65·7; H, 5·2%). The 2 : 4-*dinitrophenylhydrazone* crystallised from glacial acetic acid as orange needles, m. p. 210—211° (Found: N, 9·85. $C_{27}H_{24}O_{10}N_4$ requires N, 9·9%).

3-*Benzyloxyacetyl*-5 : 6 : 7-*trimethoxy*iso*coumarin Diethyl Mercaptal.*—Anhydrous sodium sulphate (1·5 g.) was added to a solution of the above α-benzyloxy-ketone (0·5 g.) and zinc chloride (1·5 g.) in ethanethiol (30 c.c.). When the mixture had stood for 18 hr. in ice, excess of ethanethiol was removed under reduced pressure and the residue shaken with 0·5N-hydrochloric acid and ether. The ethereal layer was washed with water and dried (Na_2SO_4) and the solvent removed under reduced pressure. The residual pale yellow pungent oily diethyl mercaptal, which was used as such in subsequent work, was readily decomposed by heat and gave a precipitate with alcoholic mercuric chloride.

3-*Benzyloxyacetyl*-5 : 6 : 7-*trimethoxy*iso*coumarin Ethylene Mercaptal.*—Dry hydrogen chloride was passed through a suspension of anhydrous sodium sulphate (1·5 g.) and the above α-benzyloxy-ketone (III; R = $CO{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$) (0·5 g.) in a mixture of dioxan (10 c.c.) and ethanedithiol (0·15 c.c.). After 3 hr. the supply of hydrogen chloride was discontinued and the mixture, now bright red, was set aside overnight, then poured into water and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4) and the solvent removed; the residual *ethylene mercaptal* crystallised from ethanol as a mat of fine needles, m. p. 133—134° (Found: C, 60·3; H, 5·2; S, 14·1. $C_{23}H_{24}O_6S_2$ requires C, 60·0; H, 5·2; S, 13·9%).

3-*Ethyl*-5 : 6 : 7-*trimethoxy*iso*coumarin* (III; R = Et).—A solution of either mercaptal (1·0 g.) in ethanol (100 c.c.) was refluxed with Raney nickel (12 g.) for 18 hr. The solvent was decanted and the nickel washed successively with ethanol (3 × 100 c.c.) and acetone (5 × 100 c.c.). These washings and the reaction solution were combined and centrifuged, and the solvent was removed, leaving a pale yellow residue (0·3 g.) which was dissolved in benzene (25 c.c.) and chromatographed on alumina (10 g.). Elution with benzene yielded, on evaporation, colourless crystals (0·2 g.) of 3-*ethyl*-5 : 6 : 7-*trimethoxy*iso*coumarin* (III; R = Et) which recrystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 69—70° (Found: C, 64·0; H, 5·9. $C_{14}H_{17}O_5$ requires C, 63·7; H, 6·1%). No further crystalline material could be eluted with benzene, ether, or acetone.

The 3-ethyl*iso*coumarin, m. p. 69—70° (0·08 g.), was heated with methanolic ammonia (3 c.c.) in a sealed tube at 120° for 3 hr. The solution was evaporated to dryness, yielding 3-*ethyl*-5 : 6 : 7-*trimethoxy*iso*carbostyril* as a white solid (0·07 g.) which crystallised from methanol in long colourless needles, m. p. 171—171·5° (Found: N, 4·8. $C_{14}H_{17}O_4N$ requires N, 5·3%).

3 : 4-*Dihydro*-3-2′-*hydroxyethyl*-5 : 6 : 7-*trimethoxy*iso*coumarin* (II; R = $CH_2{\cdot}OH$).—Decarboxylated trimethyl*iso*galloflavin (Haworth and McLachlan, *loc. cit.*) (0·25 g.) was dissolved in 90% acetic acid (30 c.c.) and shaken with palladous oxide (0·02 g.) in hydrogen at 50° and atmospheric pressure. Hydrogen uptake (65 c.c.; calc., 64 c.c.) was complete in 2 hr. The catalyst and solvent were removed, and the hexahydro-derivative crystallised from benzene–light petroleum (b. p. 60—80°) in needles (0·15 g.), m. p. 83—84° undepressed on admixture with an authentic specimen but depressed to 70—75° on admixture with the tetrahydro-derivative (IV), m. p. 82—83°.

tert.-*Butyl* 5 : 6 : 7-*Trimethoxy*iso*coumarin*-3-*ylacetate* (III; R = $CH_2{\cdot}CO_2Bu^t$).—A freshly filtered solution of silver benzoate (1 g.) in triethylamine (7 c.c.) was added portionwise during 1½ hr. to a boiling solution of 3-diazoacetyl-5 : 6 : 7-trimethoxy*iso*coumarin (2 g.) in dry *tert.*-butanol (50 c.c.). Refluxing was continued for a further ½ hr.; then the excess of silver salts was decomposed with a little formic acid, and the mixture treated with charcoal, filtered, and evaporated to a brown resin. The resin was chomatographed in benzene (25 c.c.) on alumina (50 g.). Elution with benzene yielded, on evaporation, colourless crystals closely followed by a red oil. Recrystallisation of the first eluant from *cyclo*hexane afforded tert.-*butyl* 5 : 6 : 7-*trimethoxy*iso*coumarin*-3-*ylacetate* (1·0 g.) as stout needles, m. p. 100—101° (Found: C, 61·2; H, 6·4. $C_{18}H_{22}O_7$ requires C, 61·7; H, 6·3%).

Methyl 5 : 6 : 7-*Trimethoxy*iso*coumarinyl*-3-*acetate* (III; R = $CH_2{\cdot}CO_2Me$).—The above *tert.*-butyl ester (0·12 g.) was dissolved in a mixture of acetic acid (3 c.c.), concentrated hydrochloric acid (1 c.c.), and water (1 c.c.), and the solution was refluxed for 2 hr. The resulting dark brown solution was diluted with water and extracted with ether. The ethereal extract was washed with water and sodium hydrogen carbonate solution. Acidification of the

carbonate extract gave an amorphous acid (0·03 g.). This acid, isolated with ether, was dissolved in methanol and methylated with excess of ethereal diazomethane. The methyl ester crystallised from benzene–light petroleum (b. p. 60—80°) as prisms, m. p. 127—128° (Haworth, Pindred, and Jefferies, *loc. cit.*, give m. p. 127—128°).

3 : 4-*Dihydro*-5 : 6 : 7-*trimethoxyisocoumarin*-3-*ylacetic Acid* (II; R = CO_2H).—(*a*) The above *tert.*-butyl ester (0·84 g.) was shaken in glacial acetic acid (25 c.c.) with 25% palladium–charcoal in an atmosphere of hydrogen at 50° and atmospheric pressure. Hydrogen uptake (57 c.c.; calc., 57 c.c.) was complete after 12 hr. Removal of the catalyst and solvent gave a viscous syrup which was hydrolysed by 2 hours' refluxing with acetic acid (15 c.c.), concentrated hydrochloric acid (5 c.c.), and water (5 c.c.). Evaporation of the solvent under reduced pressure gave 3 : 4-*dihydro*-5 : 6 : 7-*trimethoxyisocoumarin*-3-*ylacetic acid* as a pale yellow solid, crystallising from 5% acetic acid solution in colourless rhombs (0·6 g.), m. p. 155—156° [Found: C, 57·1; H, 5·6%; equiv., 294 (cold), 147·5 (hot). $C_{14}H_{16}O_7$ requires C, 56·8; H, 5·4%; equiv., 296 (cold), 148 (hot)].

(*b*) 3 : 4-Dihydro-3-2′-hydroxyethyl-5 : 6 : 7-trimethoxy*iso*coumarin (II; R = CH_2·OH) (85 mg.) was dissolved in a mixture of acetic acid (1 c.c.), water (3 c.c.), and concentrated sulphuric acid (0·5 c.c.). A solution of potassium dichromate (70 mg.) in a little 10% acetic acid was added dropwise during 2 hr. to the cooled solution. The mixture was then warmed on a water-bath for 30 min. to complete the reaction, diluted with water, and continuously extracted with ether for 3 hr. The ethereal extract was evaporated to dryness, and the residue redissolved in ether, and extracted with sodium hydrogen carbonate solution. Acidification of the carbonate extract followed by extraction with ether and evaporation of the solvent left the *acid* (45 mg.) which crystallised from dilute acetic acid (5%) in small rhombs, m. p. 155—156° (Found: C, 56·7; H, 5·8), undepressed on admixture with 3 : 4-dihydro-5 : 6 : 7-trimethoxy*iso*coumarinyl-3-acetic acid (II; R = CO_2H) obtained by method (*a*).

Prepared by either method, the acid when crystallised from its cold supersaturated dilute acetic acid solutions afforded an unstable dimorph as plates, m. p. 140—141° (with resolidification and m. p. 155—156°). Methylation of either form in methanol with ethereal diazomethane and evaporation of the solvents gave the *methyl ester* which crystallised from benzene–light petroleum (b. p. 60—80°) as small colourless rhombs, m. p. 109—110° [Found: from method (*a*), C, 57·9; H, 6·0; from method (*b*), C, 58·2; H, 5·8. $C_{15}H_{18}O_9$ requires C, 58·1; H, 5·8%]. The m. p. of the methyl ester and both forms of the synthetic acid (method *a*) were not depressed on admixture with the corresponding compounds derived by oxidation of the hexahydro-derivative (II; R = CH_2·OH) (method *b*). The m. p.s of the higher-melting forms of both synthetic and degradation acid were not depressed on admixture with the lower-melting forms of both synthetic and degradation material.

Autoxidation of Syringic Acid.—Syringic acid (0·5 g.), potassium hydroxide (0·15 g.), and disodium hydrogen phosphate (5 g.) were dissolved in water (50 c.c.), and air was blown through the solution at room temperature for 4 days, the mixture being extracted at frequent intervals with chloroform. The chloroform extracts were combined and dried ($NaSO_4$) and the solvent was evaporated, leaving a yellow solid (0·02 g.) crystallising from dilute acetic acid as needles, m. p. 250—251° undepressed on admixture with an authentic sample of 2 : 6-dimethoxy-*p*-benzoquinone (XI). Acidification of the phosphate solution precipitated syringic acid (0·21 g.) which crystallised from water as needles, m. p. 204—205°.

Action of Alkali on "Galloflavin Dipotassium Salt" (XII).—The "dipotassium salt" intermediate in the preparation of galloflavin (2 g.) was dissolved in 10% potassium hydroxide solution (36 c.c.) under nitrogen. After 45 min., the solution was acidified with hydrochloric acid and boiled for a short time. The resulting chocolate-brown precipitate (0·65 g.) was treated overnight with excess of ethereal diazomethane, the solvent removed, and the residue extracted twice with boiling methanol (20 c.c.), leaving a light brown amorphous residue (0·5 g.) (Found: OMe, 2·0%). Tetramethyl*iso*galloflavin (0·06 g.), recovered from the methanol extracts, had m. p. 222—224°, raised to 227—228° by crystallisation from methanol and gave no depression in m. p. on admixture with an authentic specimen, m. p. 232—234°.

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The Hydrolysis of Acetic Anhydride. Part IV. Catalysis by Hydrochloric Acid and the Hydrolysis of Acetyl Chloride.*

By V. Gold and J. Hilton.

[Reprint Order No. 5793.]

The rates of hydrolysis of acetic anhydride and of acetyl chloride in aqueous hydrochloric acid have been studied at 0° as a function of acid concentration over the range 0—9·28M. For acetic anhydride the rate increases steeply with acidity, whereas there is a very small decrease in the case of acetyl chloride. At the highest acid concentrations acetic anhydride is hydrolysed more rapidly than acetyl chloride. It is therefore concluded that acetyl chloride is not an intermediate in the hydrochloric acid-catalysed hydrolysis of acetic anhydride.

The reaction velocities were measured by a modification of the thermal maximum method.

It has been known for some time that the hydrolysis of acetic anhydride in aqueous solution is catalysed by hydrochloric acid and other acids (Szabo, *Z. physikal. Chem.*, 1926, **122**, 405; Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2896) but these earlier measurements do not throw much light on the mechanism of this catalysis. The problem is treated in a more general manner in Part V (succeeding paper). The present paper is concerned with an examination of the particular hypothesis that the catalysing acid HX reacts with acetic anhydride according to $Ac_2O + HX \longrightarrow AcX + AcOH$, the subsequent hydrolysis of the compound AcX being rapid compared with the hydrolysis of acetic anhydride. On general grounds this is a reasonable and attractive hypothesis. For example, there is evidence that, in anhydrous mixtures of nitric acid and acetic anhydride, acetyl nitrate is formed by this reaction (Gold, Hughes, and Ingold, *J.*, 1950, 2467), and there have been similar suggestions concerning acetyl hydrogen sulphate (Russell and Cameron, *J. Amer. Chem. Soc.*, 1938, **60**, 1345; Murray and Kenyon, *ibid.*, 1940, **62**, 1230) and acetyl perchlorate (Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159). Further, it is known that the solvolyses of acetyl chloride (Branch and Nixon *J. Amer. Chem. Soc.*, 1936, **58**, 2499) and of acetyl dihydrogen orthophosphate (Bentley, *ibid.*, 1949, **71**, 2765) are more rapid than the corresponding reactions of acetic anhydride, and Burton and Praill (*Quart. Rev.*, 1952, **6**, 302) have concluded that acetyl perchlorate is a more powerful acetylating agent than acetic anhydride.

Experimental

Materials.—Acetic anhydride (" AnalaR ") was allowed to reflux over magnesium turnings for several hours and then fractionally distilled in a dry atmosphere, a middle portion being retained for kinetic measurements. Acetyl chloride (" AnalaR ") was allowed to reflux for several hours in order to drive off hydrogen chloride, and was then distilled similarly. The hydrochloric acid solutions were prepared by dilution of " laboratory reagent as recommended for analysis." The concentration of the stock reagent was found by density determinations.

Kinetic Measurements.—Since the reactions were too rapid for investigation by conventional methods, the rate constants were obtained by a modification of the thermal maximum method of Bell and Clunie (*Proc. Roy. Soc.*, 1952, *A*, **212**, 16; cf. Bell, Gold, Hilton, and Rand, *Discuss. Faraday Soc.*, 1954, **17**, 151). In this modification the time taken between the mixing of the reagents and the attainment of the temperature maximum of a reaction mixture which is losing heat to its surroundings at a controlled rate is measured.

Apparatus.—Reactions vessels. The reactions were carried out in one of a matched pair of rectangular vessels of sheet platinum (4 × 4 × 16 cm.) supported in a brass frame. The vessels were placed symmetrically in the apparatus. They contained the same solution (except for the low concentration of acid chloride or anhydride in one of them) and were stirred at the same constant rate (1500 r.p.m.) by identical twisted-leaf glass stirrers driven *via* a gear box by a 1/16 h.p. constant-speed induction motor.

* Part III, *J.*, 1953, 1409.

Temperature measurement. The temperature difference between the two vessels was measured by means of a rigidly held " Pallador " thermo-couple (Messrs. Johnson, Matthey and Co. Ltd.) directly immersed in the liquid and connected across a critically damped Cambridge short-period galvanometer. This (primary) galvanometer gave a deflection of 1 cm./0·1°, and approximately 30-fold sensitivity was obtained by means of a simple photo-amplifier in which the light reflected by the primary galvanometer was made to fall on a knife edge and then on to a high-impedance " Cintel " photo-cell which, in turn, actuated a secondary critically damped galvanometer (Tinsley, short-period). The optical arrangement was such that the movement of the primary galvanometer mirror did not change the position of the illuminated area of the photo-cell electrode, and that the intensity of illumination of the photo-cell was strictly proportional to the deflection of the primary galvanometer. The light source for the primary galvanometer was a Mazda Exciter lamp (Projection lamp, Class G, Exciter G/8) run off a stabilised mains supply stepped down to 8 v.

For calibration purposes a current of about 0·03 μA could be passed through the primary galvanometer from two Weston cadmium cells with a 60-megohm resistance in series. The use of twin vessels ensures that both junctions are exposed to identical influences, in particular to the same heat of stirring which causes an appreciable temperature rise above the temperature of the bath in solutions of high viscosity.

Temperature control. The temperature of the bath was kept constant at 0° by water in contact with a large mass of ice, generated as a frozen sheet at the bottom of the tank by pumping refrigerant liquid (temperature $< -3°$) through 10 ft. of copper tubing. The thermostat liquid was agitated by a circulating pump driven by a second constant-speed motor, which pumped a steady flow of liquid past the two platinum vessels, and by rotary blades attached to the extended shaft of the centrifugal pump, substantially as in the single-vessel apparatus of Bell and Clunie (*loc. cit.*).

Mixing of reagents. Acetic anhydride or acetyl chloride was injected into the stirred reaction mixture from an all-glass syringe with an outlet 0·02 cm. in diameter. The narrow outlet ensured that there was no interdiffusion of liquids in the capillary and allowed the reactant to enter in a finely divided form, thus hastening solution. The construction was such that the reservoir of injected liquid was below the level of the liquid in the reaction vessel, thus ensuring that the reagent was at the same temperature as the solvent. Since the reaction time was short compared with the time necessary for the transfer of heat through the wall of the reservoir, no measurable temperature effect was produced by the replacement of the injected reagent by reagent not previously below this level. This method of mixing suffers from the drawback that a time of the order of $\frac{1}{2}$ sec. is required for the injection. The zero-time for the reaction was taken half-way between starting and finishing the injection. Since the concentration of injected reagent was low (~0·01M), several runs could be made in succession without changing the solvent.

Assembly. The construction of all non-rigid parts allowed their accurate re-alignment. The galvanometer circuits were screened, and all vessels, screens, and other metallic components were connected to earth. A platinum heating coil was incorporated in the reaction vessel to allow the determination of the effective water equivalent of the system and calibration of the thermocouple.

Procedure.—For the determination of the cooling constant the temperature of the acid in the reaction vessel was raised 0·4—0·6° above the equilibrium temperature by withdrawing about 20 ml. of the acid from the vessel into a pipette whose bulb was warmed by hand and then returning it to the vessel (or else by electrical heating). When the excess temperature had fallen to 0·15°, readings of the secondary galvanometer were taken at 6-sec. intervals, and the first-order cooling constant $[k_2 = -(1/T_{excess})dT/dt]$ calculated by Guggenheim's method. For each acid the value of the cooling constant was determined 4—8 times, and a mean value taken.

For carrying out reactions sufficient reactant was injected to cause a maximum temperature rise (T_m) of 0·1° or slightly less. Readings of the secondary galvanometer were taken for about three times the time needed to reach the maximum (t_m). The time t_m was estimated from a graph of the experimental points (Fig. 1). As a rule, three values of t_m were measured and their agreement was within ±3%.

It was verified by numerical calculation that, if the galvanometer system is critically damped and the time taken to reach 90% of full deflection—when an e.m.f. is applied instantaneously—is less than about one-fifth of the value of t_m, the inertia of the galvanometer system is insignificant and the observed maximum of the deflection is practically synchronous with the temperature maximum. For faster reactions the measurement of T_m, rather than t_m, is to be preferred.

Theory.—The time of attainment of maximum temperature (t_m) for an exothermic first-order reaction is given by

$$t_m = \frac{1}{(k_2 - k_1)} \ln \left[\frac{k_2}{k_1} \left(1 + \frac{T_i}{T_0} - \frac{k_2 T_i}{k_1 T_0} \right) \right] \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

[Bell and Clunie's equation (3), *loc. cit.*], where T_0 is the rise in temperature due to the reaction which would be observed under adiabatic conditions, T_i is the initial instantaneous rise in temperature due to the heat of mixing of the reactants, k_1 is the rate constant of the reaction, and k_2 is the cooling constant. The ratio T_i/T_0 ($\equiv \rho$) may be found or eliminated from this expression by carrying out each experiment twice in vessels with different cooling constants. A reduction of about 30% in k_2 could be achieved by masking two of the external faces of the reaction vessel with Perspex spacers. It was shown in this way that, for the reactions considered, ρ is of the order of $+0{\cdot}1$ to $+0{\cdot}2$. Procedures for the determination of T_i and T_0 have been described in previous papers on this method. In the present investigation the precise determination of T_i

FIG. 1. *Temperature–time curves of the thermal maximum method. (Hydrolysis of acetyl chloride in water at 0°.)*

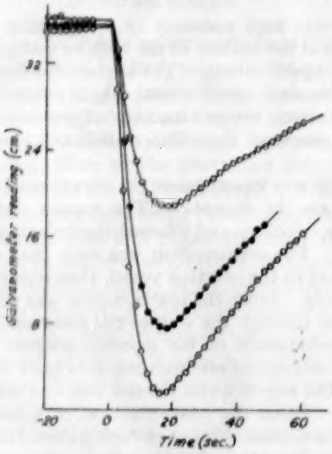
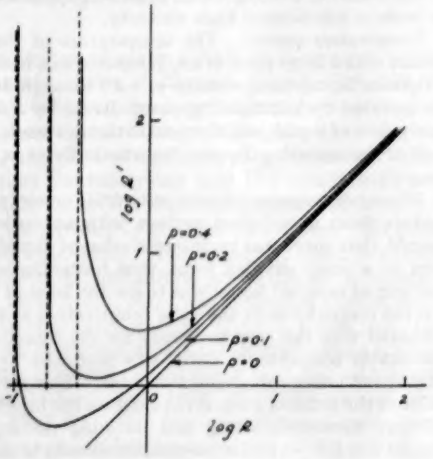


FIG. 2. *Relation between R and R'.*



is difficult, and since the highest accuracy attainable by the method was not required, a less rigorous and experimentally much easier approach was adopted. From this point of view the following examination of equation (1) is profitable.

Let k' be defined by the equation

$$t_m = [1/(k_2 - k')] \ln k_2/k' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and let $R' = k'/k_2$ and $R = k_1/k_2$. When $\rho = 0$, $k' = k_1$; for other values of ρ, k' will deviate from k_1, and therefore R' from R. The manner in which R' and R diverge has been calculated numerically for different values of ρ and is shown in Table 1 and Fig. 2. It is seen that as $R \longrightarrow \infty$, $R' \longrightarrow R$, but that there is a large difference between R' and R for low values of R.

The values of k' in Tables 2 and 3 were derived from the experimentally observed t_m values by solution of equation (2). For acetic anhydride the range of R' covered is from 1 to 28 approximately. From the systematic variation of R' with acidity it may be concluded that only the higher root of R need be considered. It will be seen from Table 1 that for the fastest of these reactions R' will exceed R by 10% at the most, and that, for the slowest of these reactions it is possible that R is less than R' by as much as 35% of the value of R'. For acetyl chloride R is in the range 5—9. Since, in this case, we do not have a systematic variation of the observed value with acidity it is possible that the found value of R' corresponds to either one of two possible values of R. The lower of these two values corresponds to a reaction velocity which is slow enough for measurement by conventional methods. Since it is known that the hydrolysis of acetyl chloride is too fast for such measurements, only the higher value of R has significance in this case.

It is assumed in the calculation that the hydrolysis reaction is kinetically of the first order. This is reasonable, since the hydrolysed reagent is in both reactions the only component of the reaction mixture whose concentration is expected to vary significantly during the course of the reaction. A first-order law has been found to be rigorously obeyed in all similar reactions where the progress of the reaction can be followed with precision. The assumption is further justified

TABLE 1. *The relationship between* R *and* R′ *for different values of* ρ.

	R′				R′				R′		
R	ρ = 0·1	ρ = 0·2	ρ = 0·4	R	ρ = 0·1	ρ = 0·2	ρ = 0·4	R	ρ = 0·1	ρ = 0·2	ρ = 0·4
0·5	0·72	1·13	5·84	4·0	4·37	4·75	5·59	32·0	33·2	34·4	36·5
1·0	1·23	1·54	2·58	8·0	8·52	9·03	10·08	64·0	65·9	67·8	71·2
2·0	2·28	2·60	3·39	16·0	16·7	17·5	19·0				

by the absence of any dependence of t_m upon the initial concentration of hydrolysed reagent (see Fig. 1). In both cases the identification of the observed rate process with the hydrolysis reaction is supported by a variety of circumstantial evidence. The case of acetic anhydride is discussed more fully in Part V.

Results are summarised in Tables 2 and 3.

TABLE 2. *The hydrolysis of acetic anhydride in aqueous hydrochloric acid at* 0°.

$[Ac_2O]_{initial}$ = 0·01—0·04M.

[HCl] (M)	$-H_0$ *	t_m,(1) sec.	10^3k_2,(2) sec.$^{-1}$	$10^3k'$, sec.$^{-1}$	$10^3k'_{cat.}$(4)	log $k'_{cat.}$ + 5·0
0·00	—	—	—	0·046 (3)	—	—
4·64	1·37	56	1·98	1·94	1·89	3·28
5·56	1·62	42	2·21	2·60	2·55	3·41
6·50	1·89	28	2·06	5·55	5·50	3·74
6·96	2·01	22·5	1·93	8·5	8·5	3·93
9·28	2·64	6·1	2·07	56·0	56·0	4·75

TABLE 3. *The hydrolysis of acetyl chloride in aqueous hydrochloric acid at* 0°.

$[AcCl]_{initial}$ = 0·01—0·02M.

[HCl] (M)	t_m,(1) sec.	10^3k_2,(2) sec.$^{-1}$	$10^3k'$, sec.$^{-1}$	[HCl] (M)	t_m,(1) sec.	10^3k_2,(2) sec.$^{-1}$	$10^3k'$, sec.$^{-1}$	[HCl] (M)	t_m,(1) sec.	10^3k_2,(2) sec.$^{-1}$	$10^3k'$, sec.$^{-1}$
0·00	17·5	1·79	13·3	2·32	17·5	1·91	12·7	9·28	17·0	2·31	12·1
1·16	16·8	1·83	13·7	4·64	17·5	2·12	12·0				

(1) Mean of 3—6 determinations. (2) Mean of 4—8 determinations. (3) Value obtained by dilatometry. (4) $k'_{cat.} = k' - k_1°$, where $k_1°$ = first-order rate constant in water.
* Hammett's acidity function.

DISCUSSION

The results show that the hydrolysis of acetyl chloride in water is not catalysed by hydrochloric acid even in very high concentration. On the other hand, the velocity of the hydrolysis of acetic anhydride increases rapidly over the same concentration range. At concentrations of hydrochloric acid which are higher than about 7·5M, the reaction of acetic anhydride is more rapid than that of acetyl chloride (Fig. 3). These conclusions hold even if the experimental error of the method is considerably greater than that considered probable (see p. 840). If the catalysis of the hydrolysis of acetic anhydride by hydrochloric acid were due to intermediate formation of acetyl chloride, the velocity of this reaction would be expected to remain less than that for acetyl chloride and, possibly, to approach that of acetyl chloride hydrolysis asymptotically at high acidities. For this reason the catalysis by hydrochloric acid must have a different explanation.

The retardation of the rate of hydrolysis of acetyl chloride by hydrochloric acid is hardly outside the limits of experimental accuracy and cannot be given a precise interpretation. It could be due to the decreased stoicheiometric concentration of water in concentrated solutions of hydrochloric acid. It indicates that there is no common-ion retardation of the reaction by chloride ion, as found for certain types of the S_N1 mechanism.

On the basis of the present results—which are the only ones available for the hydrolysis

of acetyl chloride in water—it is impossible to draw incontrovertible conclusions concerning reaction mechanisms. The following comparison of the rates of reaction of acetyl chloride and benzoyl chloride favours the view that the reaction follows a bimolecular rather than a unimolecular mechanism. Branch and Nixon (*loc. cit.*) found that the rates of bimolecular acylation of ethanol by acetyl chloride and benzoyl chloride were in the ratio 204 : 1. The hydrolysis of benzoyl chloride in water is thought to be a predominantly unimolecular reaction (Gold, Hilton, and Jefferson, *J.*, 1954, 2756), but the bimolecular velocity constant can be approximately estimated by extrapolating the linear relation between log k and $(\varepsilon - 1)/(2\varepsilon + 1)$ (ε = dielectric constant) for low values of ε in acetone–water mixtures, in which the reaction is known to be predominantly bimolecular, to the value of $(\varepsilon - 1)/(2\varepsilon + 1)$ appropriate for water (*idem*, *ibid.*, Fig. 1). The value of the first-order rate constant for the bimolecular reaction thus found is 5×10^{-4} sec.$^{-1}$. The value of k' for acetyl chloride in water is $13{\cdot}5 \times 10^{-2}$ sec.$^{-1}$, *i.e.*, 270 times greater, and hence of the order of magnitude expected if the hydrolysis of acetyl chloride in water is indeed bimolecular.

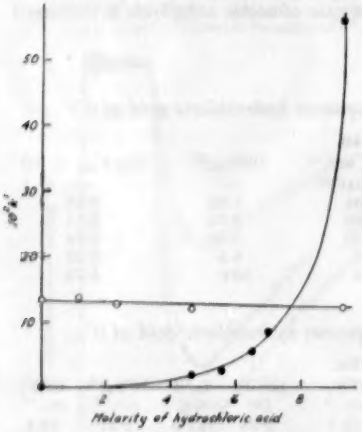


FIG. 3. *Dependence of hydrolysis velocity on concentration of hydrochloric acid.*

● Ac_2O. ○ AcCl.

The lower ionisation tendency of acetyl chloride than of benzoyl chloride is consistent with the idea that the stability of aromatic acylium ions is partly derived from the conjugation between the carbonyl group and the aromatic ring, which is impossible for aliphatic acylium ions :

This conjugation will begin to assume importance in the transition state of the ionisation reaction, and hence stability and ease of formation of acylium ions are expected to run parallel.

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The Hydrolysis of Acetic Anhydride. Part V. Catalysis by Strong Acids.*

By V. Gold and J. Hilton.

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The influence of perchloric, sulphuric, and phosphoric acid on the hydrolysis velocity has been measured over a wide range of acidity. The acids, as well as hydrochloric acid (Part IV *), have a strong catalytic effect at high concentrations. The rate increases much more rapidly than the stoicheiometric concentration of acid or of hydrogen ion. In each case, the logarithm of the rate decreases approximately linearly with Hammett's acidity function H_0, the slopes lying in the range $-0{\cdot}7$ to $-1{\cdot}3$, but there are differences in behaviour between the different acids and deviations from linearity become apparent, particularly in the cases of perchloric and sulphuric acids, for which the solutions studied cover an acidity range of 4·1 units of H_0.

The observations are held to indicate that the transition state of the reaction does not contain a water molecule and to be consistent with a mechanism in which the rate-determining step is the formation of an acetylium ion from a protonated acetic anhydride molecule.

It was suggested by Hammett (" Physical Organic Chemistry," McGraw Hill Book Co., p. 273; cf. Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791) that a proportionality between the reaction velocity of an acid-catalysed hydrolysis reaction and acidity function (h_0) is expected when the activated complex does not contain a water molecule, whereas the rate is expected to follow the stoicheiometric concentration of hydrogen ion if a water molecule is involved in the rate-determining step. The systematic application of this principle to the study of reaction mechanism, mainly by Long, has demonstrated the value of this method for a variety of reactions (hydrolysis of lactones: Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; Long, Dunkle, and McDevit, *J. Phys. Chem.*, 1951, **55**, 829; hydrolysis of methylal: Long and McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3240, 3243; depolymerisation of trioxan: Paul, *ibid.*, 1952, **74**, 141; hydration of *iso*-butene: Taft, *ibid.* p. 5372; depolymerisation of paraldehyde: Bell and Brown, *J.*, 1954, 774).

In the present investigation the dependence of the hydrolysis of anhydride upon acidity has been examined for several strong acids with the object of obtaining information concerning the mechanism of the catalysed reaction.

Experimental

Acetic anhydride was purified as in Part IV. Aqueous acids were made up from the purest samples of the acids obtained commercially. They were standardised either volumetrically or by density determinations.

Reaction velocities were determined either dilatometrically (Gold, Hilton, and Jefferson, *J.*, 1954, 2756) or by the thermal maximum method, as described in Part IV. Each dilatometric rate constant given is the mean of several determinations, agreeing within 4%. All measurements by the thermal method were repeated several times, as in Part IV. The reactions whose progress was followed dilatometrically were found to be accurately of first order, and rate constants were, as a rule, evaluated by Guggenheim's method (Fig. 1). Since the dilatometer level is sensitive to temperature changes, particular attention was paid to the elimination of the temperature difference which exists between the inside of a reaction vessel and the surrounding bath owing to the evolution of the heat of the reaction (cf. Luten, *J. Phys. Chem.*, 1935, **39**, 199; Tong and Olson, *J. Amer. Chem. Soc.*, 1943, **65**, 1704) or the attainment of the thermostat temperature after mixing. Even for a reaction with half-life as short as 2 min., the error from these sources was negligible, and significant readings could be obtained within a fraction of a minute of filling the dilatometer. It was assumed that the first-order

* Part IV, preceding paper.

kinetics continue into the region where measurements were carried out by the thermal maximum method. The rate constants obtained by this method are values of k'_1, calculated from equation (2) of Part IV. For sulphuric acid the heat of mixing (T_i) with acetic anhydride was not detectable by our methods and, accordingly, the value of k'_1 should be close to the value of the rate constant k. This conclusion is supported by the continuity of the portions of the log k–H_0 curves determined by the two methods (Fig. 2). This continuity is also fairly direct evidence that the hydrolysis reaction is the rate process observed by the thermal maximum method. In the case of perchloric acid there is an apparent break in the curves of rate constants obtained by the two methods, but the following considerations

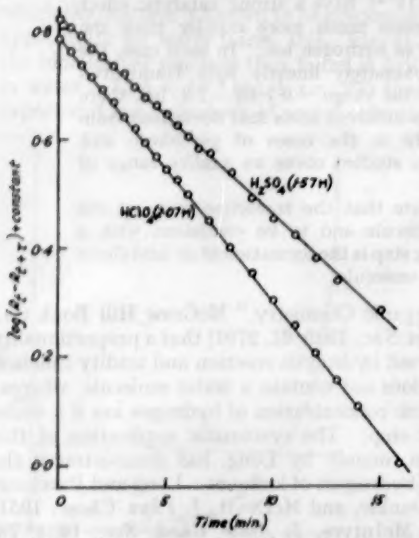

FIG. 1. *Illustration of first-order course of the hydrolysis of acetic anhydride in aqueous acids at 0°.*

show that this is almost certainly due to the neglect of T_i in the calculation of k'. It will be recalled (Part IV, Table 1, Fig. 2) that for positive values of T_i/T_0, the value of k' exceeds the value of the rate constant k, and that the deviation becomes more marked the lower the ratio (R) of the rate constant of the reaction to the Newton's law cooling constant of the vessel. For the experimental points corresponding to large values of R' (which, in this case, is a good approximation to R) it is found that there is a linear relation between log k' and H_0. The experimental points corresponding to smaller values of R' diverge from these lines in an upward direction in a similar manner to the way in which log R' diverges from log R (see Part IV, Fig. 2) if $\rho \sim 0{\cdot}15$. For this reason it is thought that no chemical significance attaches to the divergence of the lowest points (obtained by the thermal method) from the linear log k–H_0 graphs. These points have been marked † in Tables 1—3, and indicated by shading in Figs. 2 and 3. These reservations do not apply to the results at higher acidities.

Results

TABLE 1. *The hydrolysis of acetic anhydride in aqueous perchloric acid at 0°.*

A. By dilatometry.

$[Ac_2O]_{initial} = 0{\cdot}07$M (approx.).

$[HClO_4]$ (M *)	H_0	10^4k (sec.$^{-1}$)	$10^4k_{cat.}$‡ (sec.$^{-1}$)	log $k_{cat.}$ +5·0	$[HClO_4]$ (M *)	H_0	10^4k (sec.$^{-1}$)	$10^4k_{cat.}$ (sec.$^{-1}$)	log $k_{cat.}$ +5·0
0·00	—	4·60	—	—	1·29	−0·01	9·78	5·18	1·71
0·203	0·85	5·26	0·66	0·82	1·49	−0·13	11·2	6·6	1·82
0·400	0·75	5·76	1·16	1·06	1·70	−0·25	13·7	9·1	1·96
0·585	0·51	6·41	1·81	1·26	1·90	−0·35	15·7	11·1	2·05
0·775	0·36	6·95	2·35	1·37	2·07	−0·42	18·3	13·7	2·14
0·95	0·22	8·10	3·50	1·54	2·29	−0·52	22·7	18·1	2·26
1·15	0·08	9·02	4·42	1·65	2·57	−0·64	29·9	25·3	2·40

* In this and subsequent Tables, concentrations so denoted are stoicheiometric.

‡ $k_{cat.} = k_1 - k_1^\circ$ and $k'_{cat.} = k' - k_1^\circ$, where k_1° = first-order rate constant in water.

TABLE 1. *(Continued.)*

B. By thermal maximum method.

$[Ac_2O]_{initial}$ = 0·01—0·04M.

$[HClO_4]$ (M)	H_0	10^3k_2 (sec.$^{-1}$)	t_m (sec.)	$10^3k'$ (sec.$^{-1}$)	$10^3k'_{cat.}$	log $k'_{cat.}$ + 5·0
2·68	−0·68	1·36	92	0·85	0·80	2·90 †
3·12	−0·88	1·68	76	1·01	0·96	2·98 †
		1·92	70	1·02	0·97	2·99 †
3·54	−1·08	2·02	58	1·47	1·42	3·15 †
3·57	−1·09	2·00	60	1·44	1·39	3·14 †
		1·54	69	1·37	1·32	3·12 †
4·01	−1·30	1·79	48	2·45	2·40	3·38
		1·31	56	2·45	2·40	3·38
4·43	−1·51	2·04	34	4·2	4·2	3·62
5·32	−1·94	1·55	17·7	14·0	14·0	4·15
5·80	−2·20	2·10	9·2	33	33	4·52

† Points in shaded area of Figs. 2 and 3.

TABLE 2. *The hydrolysis of acetic anhydride in aqueous sulphuric acid at 0°.*

A. By dilatometry.

$[Ac_2O]_{initial}$ = 0·07M (approx.)

$[H_2SO_4]$ (M)	H_0	h_0	10^4k (sec.$^{-1}$)	$10^4k_{cat.}$ (sec.$^{-1}$)	log $k_{cat.}$ + 5·0	$[H_2SO_4]$ (M)	H_0	h_0	10^4k (sec.$^{-1}$)	$10^4k_{cat.}$ (sec.$^{-1}$)	log $k_{cat.}$ + 5·0
0·00	—	—	4·60	—	—	1·17	−0·23	1·70	11·6	7·0	1·85
0·127	0·89	0·13	5·99	1·39	1·14	1·36	−0·35	2·24	12·5	7·9	1·90
0·223	0·45	0·35	6·60	2·00	1·30	1·56	−0·47	2·95	13·8	9·2	1·96
0·443	0·28	0·52	7·87	3·27	1·51	2·05	−0·74	5·50	19·0	14·4	2·16
0·54	0·19	0·65	8·37	3·77	1·58	2·30	−0·88	7·59	24·6	20·0	2·30
0·74	0·06	0·87	9·33	4·73	1·67	2·44	−0·95	8·91	26·2	21·6	2·33
0·99	−0·12	1·32	10·6	6·0	1·78						

B. By thermal maximum method.

$[Ac_2O]_{initial}$ = 0·01—0·04M.

$[H_2SO_4]$ (M)	H_0	10^3k_2 (sec.$^{-1}$)	t_m (sec.)	$10^3k'$ (sec.$^{-1}$)	$10^3k'_{cat.}$ (sec.$^{-1}$)	log $k'_{cat.}$ + 5·0
2·96	−1·20	1·43	124	0·40	0·35	2·54 †
3·70	−1·53	1·88	83	0·72	0·68	2·83
4·44	−1·87	1·79	61	1·51	1·46	3·16
5·18	−2·21	1·83	38	3·6	3·6	3·56
5·92	−2·57	1·69	25	7·8	7·8	3·89
6·65	−2·98	1·84	14·5	17·3	17·3	4·24
7·40	−3·36	1·86	8·8	35·0	35·0	4·54

TABLE 3. *The hydrolysis of acetic anhydride in aqueous phosphoric acid at 0°.*

By thermal maximum method.

$[Ac_2O]_{initial}$ = 0·01—0·04M.

$[H_3PO_4]$ (M)	H_0	10^3k_2	t_m (sec.)	$10^3k'$ (sec.$^{-1}$)	$10^3k'_{cat.}$ (sec.$^{-1}$)	log $k'_{cat.}$ + 5·0
7·62	−1·28	1·70	70	0·82	0·77	2·89 †
8·27	−1·47	1·60	60	1·30	1·25	3·08 †
8·90	−1·69	2·05	52	1·90	1·85	3·24 †
9·54	−1·95	1·51	46	3·0	3·0	3·48
10·20	−2·15	1·64	34	4·7	4·7	3·67
10·80	−2·36	1·78	27	6·6	6·6	3·82
11·45	−2·62	1·84	19	11·5	11·5	4·06
12·72	−3·10	1·72	10	30	30	4·48

DISCUSSION

1. *The Dependence of Reaction Velocity upon Acidity.*—The relation between the logarithm of the catalytic coefficient and the acidity function H_0 is shown in Fig. 2, which includes all experimental values for acetic anhydride of the present paper and Part IV. A broken line of *unit slope* has been drawn through the points. In Fig. 3 the experimental points for the monobasic acid $HClO_4$ have similarly been plotted against log $[HClO_4]_{stoich.}$ * and, again, a straight line of unit slope has been included in the Figure (see also Part IV, Fig. 3). Although neither of the two broken lines is a perfect representation of the

* For perchloric acid, $[HClO_4]_{stoich.} \approx [H_3O^+]$ (Redlich, *Chem. Rev.*, **1946**, **39**, 333).

experimental points there can be no doubt as to which of the two is a better approximation. The catalytic coefficient is clearly not proportional to the stoicheiometric concentration of perchloric acid or hydrogen ion. The slope of the experimental points in Fig. 3 is nowhere constant and at the highest acidities exceeds the theoretical slope by a *factor* of about 9. On the other hand, log k follows the acidity function H_0 very closely at low acidities and over no significant range is the numerical value of the slope of the graph more than 30% removed from unity. The differences in behaviour of the various acids and the departures from linearity which are present, particularly at high acidities, are more in the nature of deviations from a limiting law and will be further discussed below.

These departures may seem to be more marked in the present study than in previously studied cases where a rate of dependence upon H_0 has been established, but it should also be remembered that the range of the experimental points contained in Fig. 2 (representing

FIG. 2. FIG. 3.

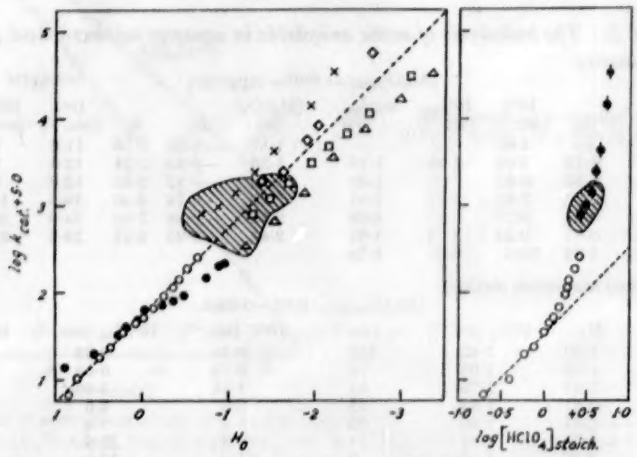

FIG. 2. *Dependence of reaction velocity on acidity function H_0.*

○ $k_{cat.}$, $HClO_4$ (dilatometry). △ $k'_{cat.}$, H_2SO_4 (thermal maximum method).
× $k'_{cat.}$, $HClO_4$ (thermal maximum method). □ $k'_{cat.}$, H_3PO_4 (,, ,, ,,).
● $k_{cat.}$, H_2SO_4 (dilatometry). ◇ $k'_{cat.}$, HCl (,, ,, ,,).

FIG. 3. *Dependence of reaction velocity on concentration of perchloric acid.*

○ Dilatometry. ● Thermal maximum method.

an approximately 10^4-fold variation in the catalysed rate) is much more extensive than is usual for this type of investigation. If the shorter (forty-fold) range of catalytic rate constants covered by the dilatometric measurements alone is considered, the deviations are much less pronounced and, if we restrict our attention to the dilatometric results for perchloric acid, the agreement with the theoretical curve is almost perfect.

2. *The Mechanism of the Catalysis.*—The observation that log k follows H_0 more closely than log $[H_3O^+]$ implies, on the basis of the principle mentioned, that a water molecule is not involved in the transition state. A water molecule would, of course, be involved for the transition state of the $A_{Ac}2$ mechanism

$$Ac_2O + H^+ \rightleftharpoons Ac_2OH^+ \text{ (rapid)}$$

$$H_2O + Ac_2OH^+ \longrightarrow (X^+) \longrightarrow CH_3{\cdot}CO_2H + CH_3{\cdot}CO_2H_2^+ \text{ etc. (rate-controlling)}$$

where (X^+) is the activated complex of the rate-controlling step. {It would be possible to reconcile approximate parallelism between log k and $-H_0$ with this mechanism if, contrary to Hammett's suggestion, it were assumed that $f_{Ac_2OH^+}/f_{X^+}$ = constant. On

that assumption, log $k_{cat.}$ for the $A_{Ac}2$ mechanism should parallel $-[H_0 - \log (H_2O)]$, which, over the concentration range studied, is not very different from $-H_0$. By analogy with the case of lactone hydrolysis this assumption concerning activity coefficients and interpretation of the mechanism seems much less likely than the conclusion that a water molecule does not participate in the rate-controlling step.}

The simplest and most probable mechanism compatible with Hammett's principle is an $A_{Ac}1$ mechanism :

$$Ac_2O + H^+ \rightleftharpoons Ac_2OH^+ \quad \text{(rapid)}$$
$$Ac_2OH^+ \longrightarrow (Y^+) \longrightarrow Ac^+ + AcOH \quad \text{(rate-controlling)}$$
$$Ac^+ + 2H_2O \longrightarrow AcOH + H_3O^+ \quad \text{(rapid)}$$

where Y^+ is the activated complex of the rate-controlling step.

3. *The Deviations from an Exact Dependence of log* k *upon* $-H_0$.—No exact interpretation can be given of the observation that there are marked differences between the behaviour of the various strong acids studied. These are only to a minor extent due to the neglect of the heat of mixing in deriving the rate constants k' for the thermal maximum method and the observations probably have a chemical basis. The following considerations seem relevant :

(a) *Temperature effect upon* H_0. For experimental reasons the velocity measurements were carried out at 0°, whereas the acidity function H_0 has been determined only for a temperature of 25°. A fuller explanation may be possible when the acidity functions at 0° are known. The temperature changes would probably affect the acidities of the various acids differently. It may be significant in this connection that the deviations of the experimental points for the viscous and associated acids, sulphuric acid and phosphoric acid, are in the direction of decreased acidity at the lower temperature, whereas the monobasic unassociated acids, hydrochloric and perchloric acids, diverge in the opposite direction.

(b) *Constancy of activity coefficient terms.* Long and McIntyre (*loc. cit.*) have focused attention on the fact the the parallelism between the acidity function and log k will only be exact in the absence of salt effects, *i.e.*, if the ratio $f_{Ac_2O}f_{BH^+}/f_{Y^+}f_B$ is exactly constant, where B,BH^+ is the conjugate acid–base pair used in the determination of the acidity function. They have shown that explicit recognition of the influence of a salt effect by the catalyst acid itself on this ratio allows an improvement in the agreement for the hydrolysis of methylal. In first approximation the modified relation between log k and H_0 may be stated in the form

$$\log k = -H_0 + (\alpha_{Ac_2O} - \alpha_B)\,[\text{Acid}] + \text{const.}$$

where α_{Ac_2O} and α_B are the salting-out parameters defined by the equation

$$\log f_B = \alpha_B \times [\text{Acid}]$$

Owing to the large spontaneous rate of hydrolysis of acetic anhydride the determination of the salting-out parameter would be very difficult and has not been carried out. Consequently, we are uncertain how great an improvement the specific inclusion of this effect would bring about. In the main it would tend to change the slope of the log k–H_0 graphs more than their curvature.

(c) *The behaviour of sulphuric acid.* It follows algebraically that if log $k + H_0$ is constant, k must be directly proportional to h_0. This direct plot is more sensitive to experimental deviations from the exact relation than the logarithmic graph, particularly at high concentration. In accordance with this expectation, the graph of k against h_0 for perchloric acid is found to be linear at the low-concentration end of the scale, the intercept passing through the ordinate at the value of k corresponding to the spontaneous rate. Fig. 2 shows that the points for sulphuric acid and for perchloric acid fall on the same line up to an acidity of $H_0 = ca.\ -0{\cdot}1$. After this, the points for sulphuric acid are lower than those for perchloric acid, but for $H_0 < ca.\ -0{\cdot}6$ a straight line of slope $-0{\cdot}93$ can be drawn through the points. The experimental points may equally well be

held to fall on two straight lines meeting at $H_0 = -1$ and having slopes of 0·64 and 0·96, respectively, or to follow an S-shaped curve. This behaviour is shown much more clearly in the graph of k against h_0 for sulphuric acid, going up to an acidity $H_0 = -1$ only (Fig. 4). {In spite of these deviations the correlation of log k with log $[H_2SO_4]$ or log $[H_3O^+]$ by using Young's data (" Record of Chemical Progress," Spring Issue, 1951, **81**) is much less satisfactory.} The chemical interpretation of these observations is not certain. They are believed to be connected with a specific effect of sulphate or bisulphate ions.

4. *The State of Acetic Anhydride in Concentrated Sulphuric Acid.*—The mechanism proposed for the acid-catalysed hydrolysis of acetic anhydride involves the rate-determining unimolecular heterolysis of the species Ac_2OH^+. The acetylium ions (Ac^+) formed by this reaction are then hydrated rapidly, *i.e.*, they do not persist in solution in appreciable concentration. As the acid concentration increases, the activity of water in the solvent decreases, and the extent to which the acetylium ions are hydrated will be governed by the equilibrium constant for the hydration reaction $Ac^+ + H_2O \rightleftharpoons AcOH_2^+$. It is not possible to decide, on the basis of the present experiments, whether this equilibrium lies to the right or to the left in 100% sulphuric acid (where the activity of water is small

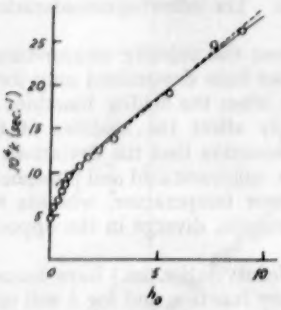

FIG. 4. *Catalytic effect of sulphuric acid at low concentrations.*

but finite owing to the self-dehydration equilibrium $2H_2SO_4 \rightleftharpoons H_3O^+ + HS_2O_7^-$) (Brand, *J.*, 1946, 585; Gillespie, *J.*, 1950, 2516). However, it is known that acetic acid produces a two-fold freezing-point depression in sulphuric acid (Hantzsch, *Z. physikal. Chem.*, 1907, **61**, 257), *i.e.*, the ion $AcOH_2^+$ is not dehydrated. This result could have the kinetic reason that the rate of the dehydration reaction is extremely small, and it is only on this basis that Gillespie's explanation of the four-fold freezing-point depression of acetic and benzoic anhydride in 100% sulphuric acid (*J.*, 1950, 2997) is intelligible. In Gillespie's paper it is assumed that $CH_3{\cdot}CO^+$ ions are not hydrated and $CH_3{\cdot}CO_2H_2^+$ ions are not dehydrated in 100% sulphuric acid. This kinetic argument does not seem attractive when it is remembered that no time effect was detected in the freezing-point of solutions of 3 : 5-dibromo-2 : 4 : 6-trimethylbenzoic acid in sulphuric acid, where acylium and acidium ions coexist (Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 708). Further, the limited number of measurements on oxygen-isotope exchange in carboxylic acids show that it is strongly acid-catalysed (Roberts, *J. Chem. Phys.*, 1938, **6**, 294; Senkus and Brown, *J. Org. Chem.*, 1938, **2**, 569) and it does not therefore seem likely that the rupture of a C–O bond is immeasurably slow in 100% sulphuric acid. These arguments suggest that the question of the state of acetic anhydride in sulphuric acid has not been settled (cf. Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 40).

We thank the D.S.I.R. for a maintenance allowance (to J. H.).

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Cyclisation of 3-*Aroyl*mesobenzanthrones *to* 4 : 5-9 : 10-*Dibenzopyrene*-3 : 8-*quinone and Its Derivatives.*

By Alan J. Backhouse and William Bradley.

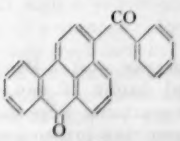
[Reprint Order No. 5869.]

A study of the action of potassium hydroxide on 3-benzoyl-, 3-*m*-nitrobenzoyl-, and 3-α-naphthoyl-*meso*benzanthrone has shown the occurrence of three concurrent reactions, (*a*) hydrolysis of acyl groups, yielding *meso*benzanthrone and a carboxylic acid, (*b*) cyclisation of the ketones to 4 : 5-9 : 10-dibenzopyrenequinone or a derivative thereof, and (*c*) nuclear hydroxylation.

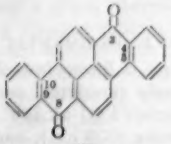
Many examples have been reported of the symmetrical union of two molecules of aromatic cyclic monoketones, such as 1 : 9-pyrazoloanthrone or *meso*benzanthrone, to form quinonoid diketones. The most general characteristic of these reactions is the coupling of carbon atoms situated *para* to carbonyl groups, the reaction depending on the presence of a strong base, such as sodioaniline or potassium hydroxide (Bradley and Bruce, *J.*, 1954, 1894). In G.P. 446,187 the self-condensation reaction has been extended to include the cyclisation of 3-α-naphthoyl*meso*benzanthrone (I; α-$C_{10}H_7$ for Ph) to a benzo-derivative of 4 : 5-9 : 10-dibenzopyrene-3 : 8-quinone (II). In this example the reaction is intramolecular and one of the nuclei becomes coupled through a carbon atom *ortho* to a carbonyl group.

In the present work the formation of a quinonoid diketone from 3-α-naphthoyl*meso*benzanthrone and potassium hydroxide has been confirmed under different conditions from those reported in G.P. 446,187, and some additional examples of the cyclisation reaction have been studied.

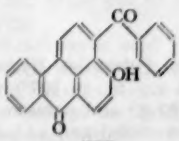
Heating 3-benzoyl*meso*benzanthrone (I) with potassium hydroxide and potassium acetate at 180° gave benzoic acid, *meso*benzanthrone, 4-hydroxy*meso*benzanthrone, violanthrone, and 4 : 5-9 : 10-dibenzopyrene-3 : 8-quinone (II), identical with the compound prepared from *meso*benzanthrone and benzoyl chloride (G.P. 412,053), or 1 : 5-dibenzoylnaphthalene (G.P. 426,710) and aluminium chloride. It is apparent that heating with alkali causes fission of (I) to benzoic acid and *meso*benzanthrone, and that the latter can yield both 4-hydroxy*meso*benzanthrone and violanthrone. Not the whole of the 4-hydroxy-derivative can arise in this way, however.



(I)



(II)



(III)

The yields of 4-hydroxy*meso*benzanthrone obtainable from *meso*benzanthrone and potassium hydroxide are known to be small in comparison with the amount of violanthrone produced (Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 259), and for this reason the much higher yields which result from the action of alkalis on (I) can arise only in some other way. The most probable explanation is that (I) yields 3-benzoyl-4-hydroxy-*meso*benzanthrone (III), by a reaction analogous to the direct hydroxylation of *meso*benzanthrone (Perkin and Spencer, *J.*, 1922, **121**, 479), which then undergoes hydrolysis with loss of the benzoyl group as benzoic acid and formation of 4-hydroxy*meso*benzanthrone. On this assumption the yields of (II) and 4-hydroxy*meso*benzanthrone obtained indicate that the relative importance of the cyclisation and hydroxylation reactions under the conditions used is 4 : 5. In other experiments manganese dioxide was added to the reactants, and this led to an increase in the amount and proportion of 4-hydroxy*meso*-benzanthrone and a reduction in the yield of 4 : 5-9 : 10-dibenzopyrene-3 : 8-quinone, the ratio cyclisation : hydroxylation being 1 : 6. The effect of manganese dioxide in aiding

hydroxylation is in agreement with the results of earlier work (Bradley, *J.*, 1937, 1791; Bradley and Waller, *J.*, 1953, 3778), and the reduction in the amount of the dibenzopyrenequinone produced indicates that (III) is an intermediate in the formation of 4-hydroxy*meso*benzanthrone, since the yield of the quinone could not be reduced by the presence of manganese dioxide unless direct hydroxylation of 3-benzoyl*meso*benzanthrone occurred and was facilitated by the addition of the oxidant.

*meso*Benzanthrone and *m*-nitrobenzoyl chloride gave two isomeric compounds, m. p. 223° and 262°, of which the first gave 4-hydroxy*meso*benzanthrone and a quinone, considered to be a nitro-derivative of (II), when heated with potassium hydroxide. For this reason the compound, m. p. 223°, was considered to be 3-*m*-nitrobenzoyl*meso*benzanthrone. The isomer, m. p. 262°, afforded a small amount of a phenolic product when heated with alkali, but there was no indication of the formation of a quinone. The compound, m. p. 262°, may be 9-*m*-nitrobenzoyl*meso*benzanthrone, since benzoyl chloride and *meso*benzanthrone afford 9-benzoyl*meso*benzanthrone as well as the 3-isomer (Moschinskaya, *Chem. Abs.*, 1941, **35**, 5488). The presence of the nitro-group greatly facilitates cyclisation, the yield of the dibenzopyrenequinone derivative being 27—28%. With 3-benzoyl*meso*benzanthrone the yield of this quinone was 10%. G.P. 412,053 describes the direct formation of nitro-derivatives of (II) from nitrobenzoyl chlorides and *meso*benzanthrone, but the formation of nitro-derivatives of (I) has not been described.

3-α-Naphthoyl*meso*benzanthrone, the preparation of which from *meso*benzanthrone-3-carbonyl chloride and naphthalene is mentioned in G.P. 446,187, on being heated with potassium hydroxide at 180° gives α-naphthoic acid, 4-hydroxy*meso*benzanthrone, and 9 : 10-benzo(4 : 5-1′ : 2′)naphthopyrenequinone. The formation of α-naphthoic acid establishes the constitution of the original naphthoyl*meso*benzanthrone as an α-naphthoyl derivative. The cyclisation reaction (yield 40%) occurred much more readily than with 3-benzoyl*meso*benzanthrone. It was first described in G.P. 446,187, in which alcoholic potassium hydroxide was used. The yield obtained by this process was not stated.

The action of potassium hydroxide and an oxidant on 4 : 5-9 : 10-dibenzopyrene-3 : 8-quinone (II) has been studied also. With manganese dioxide at 220° only a very small amount of a phenolic product was formed, probably because the hydroxylation of the quinone (II) can occur *para* to carbonyl groups only in benzene rings, and these are less readily substituted than naphthalene nuclei, as in *meso*benzanthrone (Bradley, *loc. cit.*), anthanthrone (Bradley and Waller (*loc. cit.*), pyranthrone, and *amphi-iso*pyranthrone (Backhouse and Bradley, *J.*, 1954, 4506).

Experimental

Action of Potassium Hydroxide on 3-*Benzoyl*meso*benzanthrone.*—(*a*) 3-Benzoyl*meso*benzanthrone (2 g.; m. p. 197°) was finely powdered and added during 15 min. to potassium hydroxide (20 g.) and potassium acetate (2 g.) at 150°. The reactants were stirred for 1 hr. at 180°, then cooled and added to water (500 c.c.), and the resulting suspension was filtered. The residue was extracted with 1% aqueous sodium hydroxide and the yellow alkaline solutions, which showed an intense green fluorescence, were combined and acidified. A precipitate (0·25 g.) formed and this gave a single yellow band; the product isolated therefrom had m. p. 302—304°, not depressed by 4-hydroxy*meso*benzanthrone, on sublimation *in vacuo* from a bath at 250°.

The alkali-insoluble part of the residue was heated for 1 hr. at 60—70° with a solution of sodium hydroxide (4 g.) and sodium dithionite (4 g.) in water (200 c.c.). The resulting deep cherry-red solution was filtered from undissolved solid, and on aeration for 4 hr. 4 : 5-9 : 10-dibenzopyrene-3 : 8-quinone (0·17 g.) separated. After purification by chromatography from chlorobenzene on alumina the quinone was obtained as golden-orange crystals which showed the same light absorption in 95% alcohol as the authentic compound.

The material which was insoluble in aqueous sodium hydroxide and sodium hydroxide–sodium dithionite was extracted with chlorobenzene, and the solution was chromatographed on alumina. Several bands were formed, and elution afforded (*a*) *meso*benzanthrone (0·11 g.; m. p. 172—173°); (*b*) 3-benzoyl*meso*benzanthrone (0·13 g.; m. p. 196—197°); (*c*) 4 : 5-9 : 10-dibenzopyrenequinone (0·03 g.). The chlorobenzene-insoluble solid (0·16 g.) was blue-black and showed the reactions of violanthrone.

(*b*) In a repetition of the above experiment the original alkaline filtrates were steam-distilled after acidification. Ether-extraction of the distillate gave benzoic acid (0·32 g.).

(*c*) In a further modification manganese dioxide (2 g.) was intimately mixed with the 3-benzoyl*meso*benzanthrone before the heating with the potassium hydroxide. Under these conditions the yields were: 4-hydroxy*meso*benzanthrone, 0·32 g., and 4 : 5-9 : 10-dibenzopyrenequinone, 0·05 g.

The 3-benzoyl*meso*benzanthrone used in these experiments was prepared by heating benzoyl chloride, *meso*benzanthrone, and aluminium chloride at 125° for 5 hr. (cf. Moschinskaya, *Chem. Abs.*, 1940, **34**, 1653) and chromatography of the product on alumina.

4 : 5-9 : 10-Dibenzopyrene-3 : 8-quinone was very stable to alkaline oxidants. An intimate mixture of the quinone (5 g.), manganese dioxide (5 g.), potassium hydroxide (50 g.), and potassium acetate (5 g.), stirred and heated for 1 hr. at 240°, afforded only 0·4 g. of acidic products.

3-m-*Nitrobenzoyl*meso*benzanthrone.*—*m*-Nitrobenzoyl chloride (12 g.) and an intimate mixture of *meso*benzanthrone (15 g.) and anhydrous aluminium chloride (100 g.) were stirred together and heated for 5 hr. in an oil-bath at 110°. The resulting viscous mass was cooled, crushed, and added to ice-water (1 l.), and the resulting yellow precipitate was collected, and then washed with dilute sodium hydroxide solution. The insoluble portion, dissolved in chlorobenzene and chromatographed on alumina, gave a mobile band of unchanged *meso*benzanthrone and a second band which was more strongly absorbed. This was eluted with chlorobenzene, crystallised by concentration of the eluate, and then recrystallised six times from this solvent, to give yellow crystals, m. p. 261—262·5° (Found: C, 75·8; H, 3·4; N, 3·7. $C_{24}H_{13}O_4N$ requires C, 76·0; H, 3·7; N, 3·9%), of (probably) 9-m-*nitrobenzoyl*meso*benzanthrone*. The mother-liquors from the initial chlorobenzene eluate gave a second crop of crystals on further concentration and these (0·5 g.) gave 3-m-*nitrobenzoyl*meso*benzanthrone* as yellow crystals, m. p. 223° (Found: C, 76·0; H, 3·4; N, 3·9%) after further crystallisation.

Action of potassium hydroxide. 3-*m*-Nitrobenzoyl*meso*benzanthrone (0·4 g., m. p. 223°) was stirred at 180° for 1 hr. with potassium hydroxide (10 g.) and potassium acetate (1 g.). After being cooled the melt was added to water (100 c.c.); a yellow solution having a green fluorescence was formed, from which 4-hydroxy*meso*benzanthrone (0·025 g.), m. p. 302—304°, was obtained by acidification, separation of the precipitate, and sublimation of this *in vacuo* from a bath at 250—300°. The alkali-insoluble portion of the product afforded a deep bluish-red solution on being heated at 60—70° for 1 hr. with dilute alkaline sodium dithionite. Aeration of the filtered solution gave a brown solid (0·10 g.) which was very sparingly soluble in the common solvents, gave a purple solution in concentrated sulphuric acid, and again dissolved in alkaline sodium dithionite with a bluish-red colour.

Similar treatment of the isomer, m. p. 262°, gave 0·04 g. of material which dissolved in aqueous alkali with a yellow colour and a green fluorescence, but there was no indication of the formation of a quinone reducible by alkaline sodium dithionite.

meso*Benzanthrone-3-carbonyl Chloride.*—*meso*Benzanthrone-3-carboxylic acid was prepared by hydrolysis of 3-cyano*meso*benzanthrone according to G.P. 420,412, except that the conditions used were refluxing 3-cyano*meso*benzanthrone (50 g.) with concentrated sulphuric acid (200 g.), glacial acetic acid (200 g.), and water (200 g.) for 72 hr. The yield of the 3-carboxylic acid was 15 g., m. p. 352—355°, after recrystallisation from nitrobenzene. It decomposed readily with formation of *meso*benzanthrone on being refluxed with quinoline and a small amount of copper powder.

The 3-carboxylic acid (5 g.) was refluxed for 4 hr. with chlorobenzene (100 c.c.) and thionyl chloride (10 c.c.). The resulting solution was concentrated, and the crystals formed were collected, washed with a small volume of benzene, then dried *in vacuo* (yield 4 g.). meso-*Benzanthrone-3-carbonyl chloride* had m. p. 285—290° (Found: C, 73·8; H, 3·15; Cl, 12·3. $C_{18}H_9O_2Cl$ requires C, 73·5; H, 3·1; Cl, 12·0%).

Ethyl meso*Benzanthrone-3-carboxylate.*—Prepared from the chloride and dry alcohol, or by heating the silver salt of the 3-carboxylic acid with ethyl iodide, this *ester* crystallised from alcohol in slender, dark yellow prisms, m. p. 154° (Found: C, 79·1; H, 4·8. $C_{20}H_{14}O_2$ requires C, 79·45; H, 4·7%). It dissolved in concentrated sulphuric acid with a golden-yellow colour and a green fluorescence.

3-α-*Naphthoyl*meso*benzanthrone.*—The preparation of this diketone (m. p. 244—245°; no analysis) is mentioned, but not described, in G.P. 446,187. *meso*Benzanthrone-3-carbonyl chloride (4 g.), aluminium chloride (5 g.), and naphthalene (5 g.) refluxed in carbon disulphide (200 c.c.) during 10 hr. gave, after steam-distillation followed by heating with dilute sodium hydroxide solution, a solid which was then chromatographed from chlorobenzene on alumina. The

crude *ketone* obtained by this means had m. p. 244—246° (Found: C, 87·1; H, 4·3. $C_{28}H_{16}O_2$ requires C, 87·5; H, 4·2%) after crystallisation from pyridine.

Action of fused potassium hydroxide. The ketone (0·5 g.) was finely ground, then stirred for 1 hr. at 180° with potassium hydroxide (5 g.) and potassium acetate (0·5 g.). The cooled melt was added to water, and the alkaline solution separated, acidified, and then extracted with ether. Evaporation of the extract gave a solid (0·1 g.) which, after recrystallisation from water, had m. p. 150—154°, not depressed by α-naphthoic acid, but depressed by β-naphthoic acid. The acidified aqueous solution contained a precipitate (0·1 g.), which, after collection, washing, and drying was sublimed *in vacuo* from a bath at 250—300°. The bright yellow sublimate had m. p. 300—304°, not depressed by 4-hydroxy*meso*benzanthrone.

The material which remained undissolved when the original melt was added to water was collected, washed, and heated at 60—70° for 1 hr. with a solution of sodium hydroxide (1 g.) and sodium dithionite (1 g.) in water (50 c.c.). The resulting carmine-red solution was filtered and then aerated. The precipitate of 9 : 10-benzo(4 : 5-1′ : 2′)naphthopyrene-3 : 8-quinone (0·2 g.) which formed was collected and chromatographed from chlorobenzene on alumina. The main orange band on elution with chlorobenzene gave crystals, m. p. 356—368° (Found: C, 87·5; H, 3·7. Calc. for $C_{28}H_{14}O_2$: C, 87·9; H, 3·7%). These dissolved in concentrated sulphuric acid with a dark blue colour similar to that reported for the product (no analysis recorded) obtained by the action of potassium hydroxide in alcohol at 100—230° (G.P. 446,187).

We thank Imperial Chemical Industries Limited, Dyestuffs Division, for a maintenance grant to one of us (A. J. B.) and for gifts of *meso*benzanthrone.

CLOTHWORKERS' RESEARCH LABORATORY,
UNIVERSITY OF LEEDS. [*Received, November 10th*, 1954.]

Some Compounds related to 1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine.*

By DAVID J. DRAIN and DONALD E. SEYMOUR.

[Reprint Order No. 5800.]

A series of compounds derived from 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine by replacement of one or both oxygen atoms by sulphur has been prepared for testing against *Mycobacterium tuberculosis*. Several related phthalazines are described.

As part of a research relating to the chemotherapy of tuberculosis, 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (I; R = OH, X = O) was prepared and found to exhibit fairly high tuberculostatic activity both *in vitro* and *in vivo* (Bavin, Drain, Seiler, and Seymour, *J. Pharm. Pharmacol.*, 1952, **4**, 844). Although this compound has usually been regarded as existing in the keto-form (II; X = Y = O) the hydroxyphthalazone structure (I; R = OH, X = O) will be used throughout this paper, both for uniformity of nomenclature and because it more truly represents the properties and reactions of the compound.

Because of a certain resemblance between the structure of this compound and that of the tuberculostatic thiosemicarbazones, it was of interest to investigate the biological activity of a series of related compounds in which one or both of the oxygen atoms were replaced by sulphur.

Treatment of 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine with phosphorus pentasulphide in xylene gave the diphthalazinyl sulphide (III; X = Y = S) in addition to the expected 1 : 2-dihydro-4-mercapto-2-phenyl-1-thiophthalazine (I; R = SH, X = S). On oxidation with hydrogen peroxide in alkaline solution the former product was converted

into the corresponding diketo-sulphide (III; X = O, Y = S) which on further oxidation with hydrogen peroxide in acetic acid yielded the diketo-sulphone (III; X = O, Y = SO_2). The thio-thiol (I; R = SH, X = S) was readily alkylated by treatment of its sodium derivative with alkyl halides, and its structure was confirmed by conversion of its *S*-benzyl derivative (I; R = S·CH_2Ph, X = S) with alkaline hydrogen peroxide into the corresponding oxo-compound (I; R = S·CH_2Ph, X = O) also obtained by reaction of 4-chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (I; R = Cl, X = O) with sodium benzyl sulphide.

4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (I; R = Cl, X = O) was readily prepared by the action of phosphoryl chloride on (I; R = OH, X = O). Reaction with sodium alkoxides or sodium alkyl sulphides gave the corresponding alkoxy- or alkylthio-compounds in good yields. The preparation of the alkoxy-compounds by alkylation of (I; R = OH, X = O) was described by Rowe, Gillan, and Peters (*J.*, 1935, 1808) and their formulation of these compounds as *O*-alkyl rather than *N*-alkyl derivatives is confirmed by the above method of preparation.

The chloro-compound with potassium hydrogen sulphide in refluxing ethylene glycol (no reaction occurred in boiling ethanol) yielded 1 : 2-dihydro-4-mercapto-1-oxo-2-phenylphthalazine (I; R = SH, X = O).

Treatment of the 4-alkoxy-compounds (I; R = OAlk, X = O) with phosphorus pentasulphide in boiling xylene yielded a series of 4-alkoxy-1 : 2-dihydro-2-phenyl-1-thiophthalazines (I; R = OAlk, X = S). De-ethylation of the ethoxy-compound gave, in good yield, 1 : 2-dihydro-4-hydroxy-2-phenyl-1-thiophthalazine (I; R = OH, X = S).

Experimental

1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine* (I; R = OH, X = O).—Refluxing equimolar quantities of phenylhydrazine and phthalic anhydride for 24 hr. in ethanol yielded 79% of *N*-anilinophthalimide together with 11% of 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (cf. Biquard and Grammaticakis, *Bull. Soc. chim. France*, 1942, **9**, 657, who claim a good yield of the phthalazine by an identical method). *N*-Anilinophthalimide was rearranged to 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine in 92% yield by ethanolic sodium ethoxide (Chattaway and Tesh, *J.*, 1920, **117**, 711).

4-*Chloro*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = Cl, X = O).—1 : 2-Dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (20 g.) in phosphoryl chloride (20 c.c.) was heated under reflux for 4 hr., and the mixture poured into 5N-sodium hydroxide (200 c.c.) containing crushed ice. After 1 hr. the solid (17·8 g.; m. p. 124—127°) was collected, washed with water, and recrystallised from aqueous ethanol from which the *chloro*-compound separated as needles, m. p. 130° (Found: C, 65·3; H, 3·45; N, 10·7; Cl, 14·2. $C_{14}H_9ON_2Cl$ requires C, 65·6; H, 3·5; N, 10·9; Cl, 13·9%).

Reaction of* 1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine with Phosphorus Pentasulphide.—1 : 2-Dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (11·9 g.) in dry xylene (200 c.c.) was refluxed with stirring for 6 hr., during which phosphorus pentasulphide (11·1 g.) was added in six portions. The hot solution was decanted from a small residue and allowed to cool overnight, the yellow crystals which had separated [Solid (A); 4·1 g.; m. p. 250—254°] were collected, and the xylene liquors (B) worked up as described below. Solid (A) was triturated with dilute aqueous sodium hydroxide, and the insoluble material (2·9 g.) was recrystallised from acetic acid from which *di*-(1 : 2-*dihydro*-2-*phenyl*-1-*thio*-4-*phthalazinyl*) *sulphide* (III; X = Y = S) separated as orange needles, m. p. 256·5° (decomp.) (Found: C, 66·8; H, 3·35; N, 10·5; S, 19·1. $C_{28}H_{18}N_4S_3$ requires C, 66·4; H, 3·55; N, 11·1; S, 19·0%). The xylene liquors (B) were steam-distilled to remove xylene, and the residue, an orange-red oil which solidified, was ground with dilute sodium hydroxide solution. Acidification of the alkaline filtrate gave a yellow solid (2·5 g.) which after two recrystallisations from alcohol yielded yellow needles, m. p. 167—168°, of **1 : 2-*dihydro*-4-*mercapto*-2-*phenyl*-1-*thiophthalazine*** (I; R = SH, X = S) (Found: C, 62·8; H, 3·7; N, 10·4; S, 22·4. $C_{14}H_{10}N_2S_2$ requires C, 62·2; H, 3·7; N, 10·4; S, 23·7%).

Di*-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *Sulphide (III; X = O, Y = S).—To a suspension of di-(1 : 2-dihydro-2-phenyl-1-thio-4-phthalazinyl) sulphide (0·27 g.) in ethanol (100 c.c.) at 60°, 30% hydrogen peroxide (2 c.c.) was added, followed by methanolic 2N-potassium hydroxide (3 c.c.). After 1 hr. at 60° the mixture was evaporated to dryness *in*

vacuo, the residue triturated with water, and the solid collected (0·23 g.). After two recrystallisations from alcohol *di*-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *sulphide* formed yellow needles, m. p. 198—200° (Found : C, 70·45; H, 3·7; N, 11·5; S, 7·1. $C_{28}H_{18}O_2N_4S$ requires C, 70·9; H, 3·8; N, 11·8; S, 6·75%).

Di-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *Sulphone* (III ; X = O, Y = SO_2).—Di-(1 : 2-dihydro-1-oxo-2-phenyl-4-phthalazinyl) sulphide (0·2 g.) in acetic acid (10 c.c.) was heated at 100° with hydrogen peroxide (2 c.c. of 30%). An orange colour, formed initially, faded after a few seconds to give a colourless solution from which crystals soon began to separate. After 1 hr. the mixture was cooled and the product (0·2 g. ; m. p. 262—264°) collected. On crystallisation from acetic acid *di*-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *sulphone* was obtained as feathery needles, m. p. 265° (Found : C, 65·0; H, 3·8; N, 10·9; S, 6·2. $C_{28}H_{18}O_4N_4S$ requires C, 66·4; H, 3·55; N, 11·1; S, 6·3%).

4-*Benzylthio*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (I ; R = S·CH_2Ph, X = S).—1 : 2-Dihydro-4-mercapto-2-phenyl-1-thiophthalazine (0·27 g.) in ethanol (5 c.c.) was treated with ethanolic N-sodium ethoxide (1 c.c.) followed by benzyl chloride (0·126 g.). After 1 hour's heating under reflux the solution was cooled and the yellow crystals (0·32 g. ; m. p. 134°) were collected and washed with water to remove inorganic material. After recrystallisation from ethanol, 4-*benzylthio*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* separated as yellow needles, m. p. 135° (Found : C, 70·4; H, 4·7; N, 7·8; S, 17·5. $C_{21}H_{16}N_2S_2$ requires C, 70·0; H, 4·45; N, 7·8; S, 17·8%). Similarly prepared were : 4-*Ethylthio*-, yellow needles, m. p. 151°, from ethanol (Found : C, 64·1; H, 4·7; N, 9·3; S, 20·9. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4; S, 21·5%), and 4-(2 : 4-*dinitrophenylthio*)-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine*, orange prisms, m. p. 206°, from acetic acid (Found : C, 54·95; H, 2·9; N, 12·8; S, 14·6. $C_{20}H_{12}O_4N_4S_2$ requires C, 55·05; H, 2·75; N, 12·8; S, 14·7%).

4-*Benzylthio*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I ; R = S·CH_2Ph, X = O).—(*a*) To 4-chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·18 g.) in ethanol (2 c.c.) was added a solution of sodium benzyl sulphide (from 0·087 g. of the thiol), and the solution heated under reflux. After 30 min. the mixture was diluted with water till turbidity developed, and cooled to yield a solid (0·2 g.). After crystallisation from ethanol, 4-*benzylthio*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* separated as needles, m. p. 117—118° (Found : C, 73·6; H, 4·85; N, 8·1; S, 9·0. $C_{21}H_{16}ON_2S$ requires C, 73·25; H, 4·65; N, 8·15; S, 9·3%).

(*b*) 4-Benzylthio-1 : 2-dihydro-2-phenyl-1-thiophthalazine (0·18 g.) in ethanol (30 c.c.) was heated to 60° and treated with hydrogen peroxide (0·25 c.c. of 30%) followed by methanolic 2N-potassium hydroxide (0·5 c.c.). After 30 min. at 60° the solvents were removed *in vacuo* and the residue was treated with water and acidified with hydrochloric acid. The gum which separated solidified on trituration with ethanol. After recrystallisation from ethanol the compound formed needles, m. p. 116—118° undepressed on admixture with a specimen prepared by method (*a*).

4-*Ethoxy*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I ; R = OEt, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·25 g.) in ethanol (1 c.c.) was heated under reflux with ethanolic N-sodium ethoxide (1 c.c.) for 60 min. Water was added to the hot solution till turbidity developed and, on cooling, the product (0·2 g.) crystallised. After recrystallisation from light petroleum the ethoxy-compound formed needles, m. p. 104° undepressed on admixture with a specimen prepared by the method of Rowe, Gillan, and Peters (*loc. cit.*).

4-*Ethoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (I ; R = OEt, X = S).—4-Ethoxy-1 : 2-dihydro-1-oxo-2-phenylphthalazine (8·8 g.) in dry xylene (100 c.c.) was treated with phosphorus pentasulphide (7·5 g.) and heated under reflux with stirring for 1 hr. The hot solution was decanted from some gum, the xylene removed by steam-distillation, and the residual orange oil, which solidified, was crystallised from ethanol from which 4-*ethoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (8·3 g.) separated as orange-yellow rods, m. p. 153° (Found : C, 67·6; H, 5·05; N, 10·0; S, 11·3. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·9; S, 11·35%).

Similarly prepared were : 1 : 2-*dihydro*-2-*phenyl*-4-*propoxy*-1-*thiophthalazine*, yellow needles, m. p. 128°, from ethanol (Found : C, 69·3; H, 5·5; N, 9·75; S, 10·7. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·45; S, 10·8%), and 4-*butoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine*, yellow plates, m. p. 96°, from ethanol (Found : C, 69·9; H, 5·8; N, 9·0; S, 10·1. $C_{18}H_{18}ON_2S$ requires C, 69·7; H, 5·8; N, 9·0; S, 10·3%).

1 : 2-*Dihydro*-4-*hydroxy*-2-*phenyl*-1-*thiophthalazine* (I ; R = OH, X = S).—4-Ethoxy-1 : 2-dihydro-2-phenyl-1-thiophthalazine (1 g.) in acetic acid (5 c.c.) was boiled under reflux with 48% hydrobromic acid (15 c.c.) for 1 hr. After dilution with water (30 c.c.) the solution was cooled, the solid was collected and dissolved in dilute sodium hydroxide, and the solution was

filtered from a small amount of insoluble matter and acidified with hydrochloric acid. The product (0·65 g.) after recrystallisation from alcohol, formed yellow needles, m. p. 227—230° (Found: C, 66·35; H, 4·1; N, 10·7; S, 12·2. $C_{14}H_{10}ON_2S$ requires C, 66·15; H, 3·95; N, 11·0; S, 12·6%).

1 : 2-*Dihydro*-4-*mercapto*-1-*oxo*-2-*phenylphthalazine* (I; R = SH, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (2·5 g.) and potassium hydrogen sulphide (2·5 g.) in ethylene glycol (25 c.c.) were boiled under reflux for 2 hr. On cooling and dilution with water a yellow solution was obtained which on acidification gave a pale yellow solid (1·2 g.). After recrystallisation from alcohol the *mercapto*-compound formed yellow needles, m. p. 135° (Found: C, 65·8; H, 4·3; N, 10·4; S, 12·1. $C_{14}H_{10}ON_2S$ requires C, 66·15; H, 3·95; N, 11·0; S, 12·6%).

4-*Hydrazino*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = NH·NH_2, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·25 g.), hydrazine hydrate (0·5 c.c. of 100%), and hydrazine sulphate (0·25 g.) were refluxed in ethylene glycol (5 c.c.) for 3 hr. The solution was cooled and water (5 c.c.) added. The product (0·2 g.) separated as needles, m. p. 188—190°. After recrystallisation from aqueous ethylene glycol the *hydrazino*-compound formed pale yellow prismatic needles, m. p. 190° (Found: C, 66·7; H, 4·7; N, 21·9. $C_{14}H_{12}ON_4$ requires C, 66·7; H, 4·75; N, 22·2%).

The p-*nitrobenzylidene derivative* was prepared in alcohol containing a drop of acetic acid; it separated from ethanol in yellow needles, m. p. 237—238° (Found: C, 65·05; H, 4·1. $C_{21}H_{15}O_3N_5$ requires C, 65·4; H, 4·0%). Similarly prepared was the p-*acetamidobenzylidene derivative*, pale yellow, m. p. 246—247°, from aqueous ethanol (Found: C, 69·4; H, 4·75. $C_{23}H_{19}O_2N_5$ requires C, 69·5; H, 4·8%).

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The Acylation of 3-Methylcytosine.

By G. W. KENNER, C. B. REESE, and SIR ALEXANDER R. TODD.

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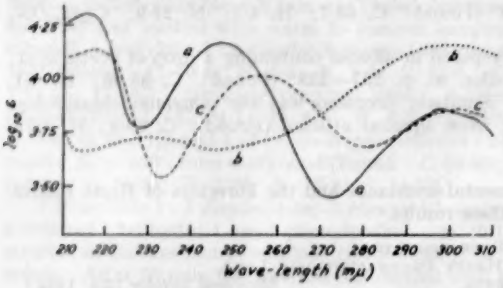
In the monoacetyl and monobenzoyl derivatives of 3-methylcytosine the acyl residue must be attached to the exocyclic nitrogen atom, since methylation by diazomethane yields the acetyl and the benzoyl derivative respectively of 1 : 3-dimethylcytosine (II; R = Me, R′ = Ac or Bz). From comparisons of spectra and dissociation constants it is deduced that 3-methylcytosine and its acyl derivatives all exist predominantly in the tautomeric form corresponding to (I) and not to (II).

MICHELSON and TODD (*J.*, 1954, **34**) have remarked that it is uncertain whether $N_{(1)}$ or $N_{(6)}$ bears the acetyl group in *N*-acetyl derivatives of cytidine. The bond between $N_{(3)}$ and the sugar residue is apparently weaker in these *N*-acetyl derivatives than in the parent bases and it therefore seemed worth attempting to resolve the ambiguity by a study of the analogous 3-methylcytosine compounds. Our investigation acquired additional interest when Flynn, Hinman, Caron, and Woolf (*J. Amer. Chem. Soc.*, 1953, **75**, 5867) announced that part of the structure of amicetin, an antibiotic, resembles that of *N*-benzoyl-3-methylcytosine, to which they assigned the structure (I; R = H, R′ = Bz) without comment. Our work now justifies the American authors' assumption and excludes the alternative structure (II; R = Bz, R′ = H).

Acetylation of 3-methylcytosine with hot acetic anhydride and pyridine gave a crystalline monoacetyl derivative, the ultra-violet absorption of which (see Figure, curve *a*) closely resembled that of *NO*$^{3'}$-diacetyldeoxycytidine (Michelson and Todd, *loc. cit.*). The same material, together with 3-methylcytosine, was produced by the reaction between 6-methoxy-3-methyl-2-pyrimidone and sodium acetimide in molten

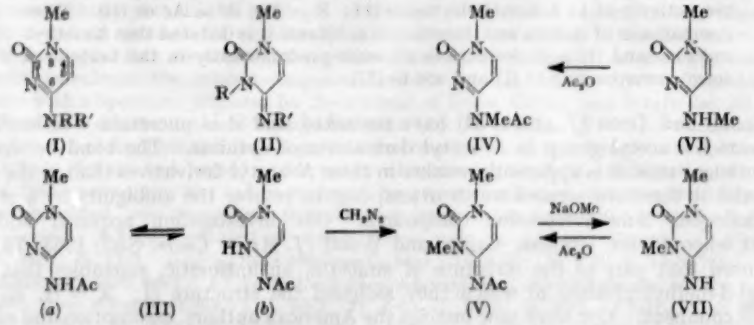
acetamide. This is consistent with its formulation as (III), but can hardly be adduced as proof of the structure since acyl migration might have occurred. An alcoholic solution of the acetyl compound reacted easily with ethereal diazomethane, giving a monomethyl derivative, m. p. 156°, with a very different ultra-violet absorption (curve *b*). This substance was converted by sodium methoxide into 1 : 3-dimethylcytosine (VII), and was shown by direct comparison to be identical with the acetyl derivative of 1 : 3-dimethylcystosine prepared by Dr. S. Varadarajan in these laboratories. The structure of 1 : 3-dimethylcytosine rests securely on the work of Hilbert (*J. Amer. Chem. Soc.*, **1934**, **56**, 190), who transformed it into 5-bromo-1 : 3-dimethyluracil, and the compound of m. p. 156° must therefore be (V). Unless acyl migration took place during the very mild diazomethane treatment, the acetyl group must be attached to $N_{(4)}$ in monoacetyl 3-methylcytosine itself which is therefore (III) and not (II; R = Ac, R′ = H). Monobenzoyl-3-methylcytosine was likewise methylated by diazomethane in alcohol and ether;



Ultra-violet spectra in ethanol:
(*a*) N^6-*acetyl-3-methylcytosine* (IIIa).
(*b*) N^6-*acetyl-1 : 3-dimethylcytosine* (V).
(*c*) N^6-*acetyl-3 : N*^{6}-*dimethylcytosine* (IV).

the product was identified by mixed melting point with the benzoyl derivative of 1 : 3-dimethylcytosine, kindly given to us by Dr. Varadarajan.

N^6-Acetyl-3-methylcytosine has two tautomeric forms (III*a* and *b*). As diazomethane substitutes a methyl group directly for an acidic hydrogen atom (Arndt, "Organic Analysis," Vol. I, p. 207, Interscience Publ., 1953), the compound (V) came from (III*b*) and it might be tempting to assume that this is the predominant tautomer. That the reverse is actually the case was shown by acetylation of 3 : N^6-dimethylcytosine (VI) and comparison of the ultra-violet spectrum (curve *c*) of the product, m. p. 196°, with the spectra of (III) and (V). The correspondence between curves *c* and *a* strongly suggests



that the compound of m. p. 196° is (IV) and that (III*a*) is the predominant tautomer. The form (III*b*) is therefore the more strongly acidic and reacts faster with diazomethane. Indeed we have been unable to obtain the compound (IV) from (III*a*); no reaction occurred when a solution of acetyl 3-methylcytosine in tetrahydrofuran was kept for two weeks with ethereal diazomethane in absence of alcohol. The situation is essentially that described as case A by Arndt (*op. cit.*, p. 211). The benzoyl series of compounds showed

the same relations of spectra, structure, and tautomerism; the structure (I; R = H, R′ = Bz) assigned by Flynn *et al.* (*loc. cit.*) to benzoyl-3-methylcytosine is therefore correct, with respect to, not only the location of the benzoyl residue, but also that of the mobile hydrogen atom.

Although our main object was the study of the acyl derivatives, we were also interested in the tautomerism of the parent 3-methylcytosine. It has recently been demonstrated in a number of instances that heterocyclic amines of the amidine type have preferentially an exocyclic amino- rather than an imino-group (*e.g.*, Angyal and Angyal, *J.*, 1952, 1461; Brown and Short, *J.*, 1953, 331). The same conclusion is drawn in the same way from physical data in the present instance. Thus 3 : N^6 : N^6-trimethylcytosine (I; R = R′ = Me) is a fairly weak base (pK_a 4·20), whereas 1 : 3 : N^6-trimethylcytosine (II; R = R′ = Me) and 1 : 3-dimethylcytosine (II; R = Me, R′ = H) (pK_a 9·29) are strong bases. Naturally the compounds capable of tautomerism, 3-methylcytosine and 3 : N^6-dimethylcytosine, adopt the more stable structure (I) and are weak bases; and their ultraviolet absorption in alcoholic solution also closely resembles that of (I; R = R′ = Me), when allowance is made for the bathochromic effect of methyl groups (cf. Brown and Short, *loc. cit.*). In acidic solution all the compounds show generally similar absorption corresponding to the resonant cation. The apparent course of *acylation*, direct substitution of an acyl residue for a hydrogen atom in (I), contrasts with Pyman's rule (*J.*, 1923, 3359) that *alkylation* of an amidine occurs at the "imino-nitrogen." Angyal (*Austral. J. Sci. Res.*, 1952, **5**, *A*, 375) has shown that sulphonyl halides do attack preferentially the ring nitrogen atoms of several heterocyclic amines and that the more stable isomer can be formed from the initial product by acyl migration. On the other hand it may be that acylation takes place *via* the resonant anion or *via* the small proportion of the strongly basic tautomer of type (II). It is noteworthy that methylation of 3 : N^6-dimethylcytosine by methyl iodide gives 1 : 3 : N^6-trimethylcytosine, whereas acetylation gives the 6-acetyl derivative.

Our principal starting material was 6-methoxy-3-methyl-2-pyrimidone, which was converted by ammonia, methylamine, or dimethylamine into the amines of type (I). 1 : 3-Dimethylcytosine (II; R = Me, R′ = H) is most conveniently made by Hilbert's method (*loc. cit.*) but can also be obtained by the action of diazomethane on 3-methylcytosine, which evidently reacts, like its acetyl derivative, as the less stable, more acidic tautomer. The importance of the 2-keto-group in promoting methylation of $N_{(1)}$ is shown by the inertness towards diazomethane of 4-acetamidopyrimidine. This compound was obtained from 2-chloro-4-methoxypyrimidine, but the method was less convenient than that described by Brown (*J. Soc. Chem. Ind.*, 1950, **69**, 353; Brown and Short, *loc. cit.*). 2-Chloro-4-methoxypyrimidine is easily accessible from 2 : 4-dichloropyrimidine owing to the greater reactivity of the chlorine at position 4 (cf. Chapman and Rees, *J.*, 1954, 1190) and its hydrogenolysis to 4-methoxypyrimidine proceeds smoothly.

During some preliminary experiments conditions were established for the conversion of 3-methyluracil into 6-chloro-3-methyl-2-pyrimidone by means of phosphoryl chloride.

Experimental

M. p.s are corrected.

3-Methylcytosine (I; R = R′ = H).—The following conditions give a slightly higher yield than those of Flynn, Hinman, Caron, and Woolf (*J. Amer. Chem. Soc.*, 1953, **75**, 5871). A solution of 6-methoxy-3-methyl-2-pyrimidone (3·5 g.; Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2005) in methanol (20 c.c.; saturated at 0° with ammonia) was heated for 8 hr. at 150°. On cooling, the product separated in large crystals (3 g.; m. p. 300°), pK_a 4·57. Light absorption in 95% EtOH : $\lambda_{max.}$ 275—276 mμ (log ε 3·85), $\lambda_{min.}$ 252 (log ε 3·64); in 0·1N-HCl : $\lambda_{max.}$ 213, 282 (log ε 4·00, 4·09), $\lambda_{min.}$ 241 (log ε 3·07).

3 : N^6-*Dimethylcytosine* (I; R = Me, R′ = H).—A solution of 6-methoxy-3-methyl-2-pyrimidone (2 g.) in 33% aqueous methylamine (14 c.c.) was heated for 8 hr. at 150°. After evaporation to dryness the 3 : N^6-*dimethylcytosine* was separated from 3-methyluracil by crystallisation from ethanol (once) and ethyl acetate (twice) and had m. p. 179°, pK_a 4·47 (Found, in material dried at 100°: C, 51·6; H, 6·5; N, 30·5. $C_6H_9ON_3$ requires C, 51·8; H,

6·5; N, 30·2%). Light absorption in 95% EtOH: $\lambda_{max.}$ 275 mμ (log ε 4·03), $\lambda_{min.}$ 251 (log ε 3·84); in 0·1N-HCl: $\lambda_{max.}$ 218, 285—286 (log ε 3·98, 4·13), $\lambda_{min.}$ 244 (log ε 3·26).

3 : N^6-*Trimethylcytosine* (I; R = R′ = Me).—Repetition of the foregoing experiment, using 35% aqueous dimethylamine instead of methylamine, gave 3 : N^6 : N^6-*trimethylcytosine* as needles, m. p. 179°, pK_a 4·20 (Found, in material dried at 80°: C, 55·0; H, 7·2; N, 27·5. $C_7H_{11}ON_3$ requires C, 54·9; H, 7·2; N, 27·4%). Light absorption in 95% EtOH: $\lambda_{max.}$ 282 mμ (log ε 4·04), $\lambda_{min.}$ 240 (log ε 3·73); in 0·1N-HCl: $\lambda_{max.}$ 221, 290 (log ε 3·93, 4·17), $\lambda_{min.}$ 247 (log ε 3·26).

1 : 3-*Dimethylcytosine* (II; R = Me, R′ = H).—A solution of 3-methylcytosine (0·2 g.) in ethanol (25 c.c.) was kept for 3 days with a solution of diazomethane (about 0·7 g.) in ether (25 c.c.). On evaporation of the solvent much unchanged material crystallised but evaporation and sublimation of the liquors at 80°/0·2 mm. gave 1 : 3-dimethylcytosine (0·03 g.; m. p. 145°, undepressed by authentic material), pK_a 9·29. Light absorption in 95% EtOH: $\lambda_{max.}$ 223, 273 mμ (log ε 4·00, 3·93), $\lambda_{min.}$ 244 (log ε 3·40); in 0·1N-HCl: $\lambda_{max.}$ 281 (log ε 4·06), $\lambda_{infl.}$ 212 (log ε 3·99), $\lambda_{min.}$ 243 (log ε 3·23).

1 : 3 : N^6-*Trimethylcytosine* (II; R = R′ = Me).—Methyl iodide (1·5 c.c.) was added to a solution of 3 : N^6-dimethylcytosine (0·36 g.) in methanol (2 c.c.). The mixture was kept in the dark for 7 days and then evaporated to a dark yellow mass, which was dissolved in the minimum of water and made alkaline with concentrated aqueous sodium hydroxide. The oil was extracted with chloroform, from which 1 : 3 : N^6-*trimethylcytosine* was obtained by evaporation and two sublimations at 45°/0·5 mm. as colourless hygroscopic crystals, m. p. 79° (Found: C, 55·3; H, 7·2; N, 27·1. $C_7H_{11}ON_3$ requires C, 54·9; H, 7·2; N, 27·4%). Its aqueous solution was strongly alkaline. Light absorption in 95% EtOH: $\lambda_{max.}$ 222, 285—286 (log ε 4·09, 3·97), $\lambda_{min.}$ 248 (log ε 3·39); in 0·1N-HCl: $\lambda_{max.}$ 212, 287 (log ε 3·81, 3·98), $\lambda_{min.}$ 248 (log ε 3·16).

N^6-*Acetyl*-3-*methylcytosine* (I; R = Ac, R′ = H).—Finely powdered 3-methylcytosine (0·5 g.) was dissolved in a boiling mixture of acetic anhydride (1·2 c.c.) and pyridine (11 c.c.), which was then kept at 100° for 1 hr. The *acetyl derivative* (0·5 g.) was collected after the mixture had been cooled to 0° and recrystallised from ethanol in needles, m. p. 268° (Found, in material dried at 100°: C, 50·5; H, 5·5; N, 25·0. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·1%). Light absorption in 95% EtOH (curve *a*): $\lambda_{max.}$ 215, 246—247, 299—300 mμ (log ε 4·30, 4·16, 3·83), $\lambda_{min.}$ 228, 272 (log ε 3·76, 3·42); in 0·1N-HCl: $\lambda_{max.}$ 214, 311 mμ (log ε 4·10, 4·19), $\lambda_{infl.}$ 224—228 (log ε 3·92), $\lambda_{min.}$ 262 (log ε 3·00).

Reaction between Sodium Acetimide and 6-*Methoxy*-3-*methyl*-2-*pyrimidone.*—A solution of sodium (0·2 g.) in methanol was evaporated to dryness. Acetamide (4·2 g.) and the pyrimidone (1 g.) were added to the residue and the mixture was kept for 1 hr. at 100°/15 mm. in a stream of nitrogen. Ammonium chloride (0·5 g.) was then added to the solution, which was cooled after 20 minutes' further heating and extracted with hot ethanol (50 c.c.). On concentration to 15 c.c. and cooling, this yielded 3-methylcytosine (0·1 g.), m. p. 294—295°. Paper chromatography of the liquor in *n*-butanol saturated with water showed that it contained approximately equal amounts of 3-methylcytosine (R_F 0·28) and of N^6-acetyl-3-methylcytosine (R_F 0·5), identified by the shape of its ultra-violet absorption curve.

N^6-*Acetyl*-3 : 6-*dimethylcytosine* (I; R = Ac, R′ = Me).—3 : 6-Dimethylcytosine (0·067 g.), acetic anhydride (0·070 g.), and pyridine (1 c.c.) were boiled until solution was complete and then kept at 100° for 1 hr. The *acetyl derivative* (0·030 g.), which separated from the cooled mixture, recrystallised from ethanol in needles, m. p. 196° (Found, in material dried at 80°: C, 53·0; H, 6·4; N, 23·4. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·1; N, 23·2%). Light absorption in 95% EtOH (curve *c*): $\lambda_{max.}$ 216, 255, 302 mμ (log ε 4·13, 4·01, 3·83), $\lambda_{min.}$ 232, 280 (log ε 3·52, 3·65).

N^6-*Acetyl*-1 : 3-*dimethylcytosine* (II; R = Me, R′ = Ac).—Diazomethane (about 1 g.) in ether (40 c.c.) was added to a solution of N^6-acetyl-3-methylcytosine (0·25 g.) in ethanol (50 c.c.). The solution was kept at room temperature for 18 hr. and then concentrated. The *product* (0·23 g.) crystallised in needles and, purified by sublimation at 90°/0·2 mm., had m. p. 156° (Found: C, 53·2; H, 6·3; N, 22·9. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·1; N, 23·2%). Light absorption in 95% EtOH (curve *b*): $\lambda_{max.}$ 228—229, 299 mμ (log ε 3·72, 4·13), $\lambda_{min.}$ 215, 244 (log ε 3·66, 3·66); in 0·1N-HCl: $\lambda_{max.}$ 214, 242, 315 mμ (log ε 4·03, 3·91, 4·14), $\lambda_{min.}$ 226, 270 (log ε 3·68, 3·21).

Deacetylation of N^6-*Acetyl*-1 : 3-*dimethylcytosine.*—The acetyl compound (0·056 g.) was heated under reflux for 2 hr. with a solution from sodium (0·02 g.) in methanol (10 c.c.). The methanol was then evaporated and the residue extracted with dry benzene, which was concentrated to small bulk and cooled. 1 : 3-Dimethylcytosine crystallised in needles (0·011 g.)

and, purified by sublimation at 80°/0·2 mm., had m. p. and mixed m. p. 147—147·5° (Found: N, 30·0. Calc. for $C_6H_9ON_3$: N, 30·2%).

N^6-*Benzoyl*-3-*methylcytosine* (I; R = Bz, R′ = H).—Finely powdered 3-methylcytosine (0·5 g.) was boiled with benzoyl chloride (0·6 c.c.) and pyridine (8 c.c.) until dissolution was complete and then kept at 100° for 1½ hr. The product (0·6 g.), which separated from the cooled solution, was recrystallised from ethanol, and had m. p. 222° (Flynn, Hinman, Caron, and Woolf, *J. Amer. Chem. Soc.*, **1953**, **75**, 5871, give m. p. 221—222°). Light absorption in 95% EtOH: $\lambda_{max.}$ 259, 304—305 mμ (log ε 4·35, 3·98), $\lambda_{min.}$ 232, 283 (log ε 4·00, 3·85).

N^6-*Benzoyl*-3: N^6-*dimethylcytosine* (II; R = Bz, R′ = Me).—3: N^6-Dimethylcytosine (0·14 g.) and benzoyl chloride (0·18 g.) were dissolved in boiling pyridine (1·3 c.c.). The solution was kept at 100° for 1 hr. before being evaporated to dryness. Recrystallisation of the residue from ethanol afforded the *benzoyl derivative* (0·03 g.), m. p. 145° (Found, in material dried at 80°: C, 64·4; H, 5·6; N, 17·6. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%). Light absorption in 95% EtOH: $\lambda_{max.}$ 265, 305 mμ (log ε 4·09, 3·94), $\lambda_{min.}$ 251, 289 (log ε 4·05, 3·87).

N^6-*Benzoyl*-1: 3-*dimethylcytosine* (II; R = Me, R′ = Bz).—Diazomethane (about 0·7 g.) in ether (25 c.c.) was mixed at room temperature with a solution of N^6-benzoyl-3-methylcytosine (0·25 g.) in ethanol (20 c.c.). After 18 hr. the solution was concentrated to small bulk. The N^6-benzoyl-1: 3-dimethylcytosine (0·2 g.), which separated on cooling, recrystallised from ethanol in needles, m. p. 156° (Found, in material dried at 60°: C, 63·9; H, 5·6; N, 17·0. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%). Light absorption in 95% EtOH: $\lambda_{max.}$ 245, 318 mμ (log ε 4·07, 4·25), $\lambda_{min.}$ 224, 270 (log ε 3·93, 3·84).

2-*Chloro*-4-*methoxypyrimidine.*—A solution of sodium (0·23 g.) in methanol (7 c.c.) was added slowly to a stirred solution of 2: 4-dichloropyrimidine (1·5 g.) in methanol (13 c.c.). After the mixture had been stirred for 40 min. further, ether (30 c.c.) was added to complete the precipitation of the salt, which was removed by filtration. Evaporation of the filtrate and crystallisation of the residue from light petroleum (b. p. 40—60°) afforded 2-*chloro*-4-*methoxypyrimidine* (0·6 g.), m. p. 55° (Found, in material sublimed at 35°/0·2 mm.: C, 41·7; H, 3·2; N, 19·3. $C_5H_5ON_2Cl$ requires C, 41·5; H, 3·5; N, 19·4%).

4-*Methoxypyrimidine.*—A solution of 2-chloro-4-methoxypyrimidine (3 g.) in methanol (25 c.c.) was shaken with magnesium oxide (1 g., "AnalaR"), 5% palladised barium sulphate (1 g.), and hydrogen (1 atm.). The theoretical quantity of hydrogen (470 c.c. at N.T.P.) was absorbed in 5 hr. The residue, obtained by filtration and evaporation, was dissolved in water (20 c.c.), which was then extracted with ether (200 c.c.). Distillation of the dried (Na_2SO_4) extract yielded 4-methoxypyrimidine (1·6 g.), b. p. 71°/33 mm. (Brown and Short, *J.*, **1953**, 336, give b. p. 69—70°/30 mm.). When a small amount was added to alcoholic picric acid, the *picrate* was immediately precipitated and, recrystallised from ethanol, had m. p. 122·5° (Found, in material dried at 60°: C, 39·1; H, 3·0; N, 20·4. $C_5H_6ON_2,C_6H_3O_7N_3$ requires C, 38·9; H, 2·7; N, 20·6%).

4-*Acetamidopyrimidine.*—A solution of 4-methoxypyrimidine (1·07 g.) in methanol (9 c.c.), saturated at 0° with ammonia, was heated at 150—160° for 7½ hr. Evaporation of the solvent gave a yellow solid mass. Acetylation of this impure 4-aminopyrimidine by Brown and Short's technique (*J.*, 1953, 337) afforded 4-acetamidopyrimidine (0·5 g.), which, sublimed at 120°/0·5 mm., had m. p. 203° (Brown and Short record m. p. 198—200°) (Found: C, 52·3; H, 5·3; N, 30·9. Calc. for $C_6H_7ON_3$: C, 52·5; H, 5·2; N, 30·6%).

6-*Chloro*-3-*methyl*-2-*pyrimidone.*—Phosphoryl chloride (8 c.c.) and 3-methyluracil (2 g.) were heated in a bath at 135° under reflux for 4½ hr. The excess of phosphoryl chloride was distilled under reduced pressure and some 2: 4-dichloropyrimidine removed by sublimation. Ice (20 g.) was added to the remaining resin, followed gradually by ammoniacal methanol until the pH rose to 8. The mixture was warmed to 30° and filtered. When kept at 0° it deposited almost pure 6-*chloro*-3-*methyl*-2-*pyrimidone* (0·63 g.), which after sublimation had m. p. 207—208° (Found: C, 41·7; H, 3·3; N, 19·1. $C_5H_5ON_2Cl$ requires C, 41·5; H, 3·5; N, 19·4%). On being heated at 150° for 8 hr. with saturated methanolic ammonia, this substance yielded 3-methylcytosine, m. p. 298° undepressed by an authentic specimen and with the same ultraviolet absorption.

We thank Dr. S. Varadarajan for samples of the acetyl and the benzoyl derivative of 1: 3-dimethylcytosine. The award of a D.S.I.R. Maintenance Allowance (to C. B. R.) is also gratefully acknowledged.

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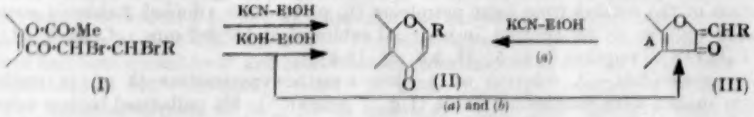
Ring Expansion of 2-Benzylidenecoumaran-3-ones—A Synthesis of Flavones.

By D. M. Fitzgerald, J. F. O'Sullivan, (Mrs.) E. M. Philbin, and T. S. Wheeler.

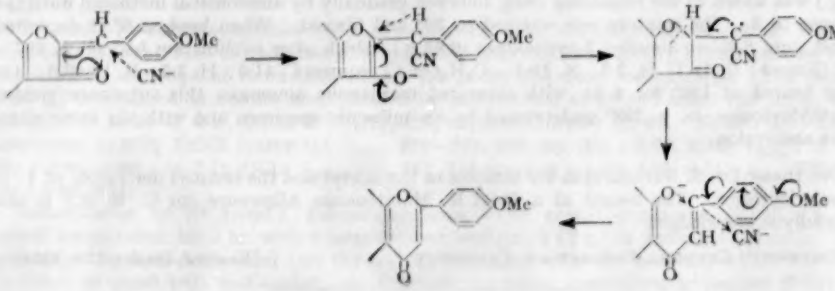
[Reprint Order No. 5849.]

The action of ethanolic potassium cyanide on certain 2-benzylidenecoumaran-3-ones gives the corresponding flavones.

Kostanecki's first synthesis of flavones (II; R = aryl) (Emilewicz and Kostanecki, *Ber.*, 1898, **31**, 696), which involves the action of ethanolic alkali on 2'-acetoxychalkone αβ-dibromides (I; R = aryl), was found by him to be of limited application. 2-Benzylidenecoumaran-3-ones (III; R = aryl) are obtained in two cases: (*a*) when R is *p*-alkoxyaryl (*idem*, *ibid.*, p. 705; 1899, **32**, 309) and (*b*) when the parent chalkone is derived from phloroacetophenone (Kostanecki and Tambor, *Ber.*, 1899, **32**, 2264). Wheeler and his collaborators (*J.*, 1937—1940, *passim*; Wheeler, *Proc. Nat. Inst. Sci. India*, 1939, **5**, 267; see also Marathey, *Science and Culture*, 1951, **17**, 86; *J. Univ. Poona*, 1952, **1**, 19) devised methods to expand the application of the Kostanecki synthesis; in particular it was shown (Hutchins and Wheeler, *J.*, 1939, 91) that with ethanolic potassium cyanide, the chalkone dibromide (as I) gave the flavone (as II) even in cases (*a*) and (*b*). In an



extension of this work, it has now been found that benzylidene compounds of type (*a*) (*i.e.* 2-*p*-alkoxybenzylidenecoumaran-3-ones; III; R = *p*-alkoxyaryl), but not those of type (*b*) (as III; ring A derived from phloroglucinol), when refluxed with excess of ethanolic potassium cyanide undergo ring expansion to form the corresponding 4'-alkoxyflavones (II; R = *p*-alkoxyaryl) in yields of over 50% (Fitzgerald, Philbin, and Wheeler, *Chem. and Ind.*, 1952, 130). Further when a limited quantity of potassium cyanide is employed to treat the chalkone dibromide (I; R = *p*-alkoxyaryl), the corresponding 2-benzylidenecoumaran-3-one (III; R = *p*-alkoxyaryl) and not the flavone (II; R = *p*-alkoxyaryl) is produced, so that in case (*a*), (III) is intermediate in the production of (II) from (I) by Hutchins and Wheeler's method. The thiocoumaran-3-one, 2-benzylidene-2 : 3-dihydro-5-methylthionaphthen-3-one (von Auwers and Arndt, *Ber.*, 1909, **42**, 541), and ω-methoxy-ω-salicylideneacetophenone (Pratt and Robinson, *J.*, 1923, **123**, 747) which has the ·CO·C(O·C):CHAr system present in 2-benzylidenecoumaran-3-ones, were unchanged after treatment with ethanolic potassium cyanide. The mechanism of the formation of flavones from 2-benzylidenecoumaran-3-ones is probably:



This synthesis recalls the Auwers synthesis of flavonols from 2-benzylidenecoumaran-3-one dibromides (von Auwers and Pohl, *Annalen*, 1914, **405**, 243), and similarly is of limited application.

Experimental

Ethanol was used for crystallisation if no solvent is mentioned.

Coumaran-3-ones used in the preparation of the 2-benzylidenecoumaran-3-ones were: 5-methylcoumaran-3-one (von Auwers and Müller, *Ber.*, 1908, **41**, 4233); 4 : 6-dihydroxycoumaran-3-one (Shriner and Grosser, *J. Amer. Chem. Soc.*, 1942, **64**, 383); 4 : 5-benzocoumaran-3-one (Ingham, Stephen, and Timpe, *J.*, 1931, 899); and 2 : 3-dihydro-5-methylthionaphthen-3-one (von Auwers and Arndt, *Ber.*, 1909, **42**, 541).

Preparation of 2-Benzylidenecoumaran-3-ones.—The following 2-benzylidenecoumaran-3-ones (numbered for reference) were prepared as described by the authors cited, or by condensing the appropriate coumaran-3-one and aldehyde by means of acid (method 1; *idem, ibid.*, p. 4238) or alkali (method 2; Sonn, *Ber.*, 1917, **50**, 1266): 2-*p*-methoxybenzylidenecoumaran-3-one (1) (Herstein and Kostanecki, *Ber.*, 1899, **32**, 319); 2-benzylidene-5-methylcoumaran-3-one (2) (von Auwers and Müller, *loc. cit.*); 2-*p*-methoxybenzylidene-5-methylcoumaran-3-one (3) (method 1), crystallised from methanol in yellow needles, m. p. 152° (Found: C, 77·1; H, 5·1. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%) (von Auwers and Anschütz, *Ber.*, 1921, **54**, 1556, give the same m. p.); 2-3′ : 4′-*dimethoxybenzylidene-5-methylcoumaran-3-one* (4) (method 1), separated in yellow plates, m. p. 174—176° (Found: C, 72·7; H, 5·2. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%); *5-methyl-2-3′ : 4′-methylenedioxybenzylidenecoumaran-3-one* (5) (method 1), crystallised from chloroform–ligroin in yellow needles, m. p. 208—210° (Found: C, 72·8; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%); 6-methoxy-2-*p*-methoxybenzylidenecoumaran-3-one (6) [Panse, Shah, and Wheeler, *J. Univ. Bombay*, 1941, (3), **10**, 84; *Chem. Abs.*, 1942, **36**, 4507]; 4 : 6-diacetoxy-2-*o*-methoxybenzylidenecoumaran-3-one (7) (Kalff and Robinson, *J.*, 1925, 1969); 4 : 6-*dihydroxy-2-o-methoxybenzylidenecoumaran-3-one* (8) (method 2), formed yellow plates, m. p. 255—260° (decomp.) (Found: C, 67·6; H, 4·0. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%); 2-3′ : 4′-*dimethoxybenzylidene-4* : 6-*dihydroxycoumaran-3-one* (9) (method 2), separated in yellow needles, m. p. 255—260° (decomp.) (Found: C, 61·2, 61·3; H, 4·7, 4·9. $C_{17}H_{14}O_6,H_2O$ requires C, 61·4; H, 4·8%); 2-p-*methoxybenzylidene-4* : 5-*benzocoumaran-3-one* (10) (method 1), crystallised in yellow needles, m. p. 168° (Found: C, 79·5; H, 4·7. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·6%); 2-3′ : 4′-methylenedioxybenzylidene-4 : 5-benzocoumaran-3-one (11) (Ingham, Stephen, and Timpe, *loc. cit.*, p. 900); 2-benzylidene-2 : 3-dihydro-5-methylthionaphthen-3-one (12) (von Auwers and Arndt, *loc. cit.*, p. 542).

Preparation of Authentic Samples of Flavones.—The authentic samples of flavones required to confirm the structures of the products of the action of ethanolic potassium cyanide on benzylidenecoumaranones were prepared as shown below. The number after the name of the flavone is that assigned above to the related benzylidenecoumaranone.

4′-*Methoxyflavone* (1). This flavone (m. p. 157—158°) was obtained by cyclisation of *p*-anisoylsalicyloylmethane (Baker and Glockling, *J.*, 1950, 2761) by using acetic acid containing a few drops of mineral acid, and by the method of von Auwers and Anchütz (*Ber.*, 1921, **54**, 1558).

Flavones numbered (3), (4), (5), and (6) were synthesised by the Baker–Venkataraman reaction. In these syntheses the intermediate compounds listed without experimental details were prepared by standard methods.

4′-*Methoxy-6-methylflavone* (3). 2-p-*Anisoyloxy-5-methylacetophenone*, which was obtained by the pyridine–acid chloride method, crystallised from methanol in plates, m. p. 116° (Found: C, 71·4; H, 5·5. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). The ester was transformed into the diketone by treatment with powdered potassium hydroxide in pyridine in the usual way, and the crude diketone was cyclised to the flavone (m. p. 170°; von Auwers and Anchütz, *loc. cit.*, p. 1556) by the hydrochloric–acetic acid method (Found: C, 76·5; H, 5·1. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%).

3′ : 4′-*Dimethoxy-6-methylflavone* (4). *5-Methyl-2-veratroyloxyacetophenone* separated from methanol in plates, m. p. 119° (Found: C, 68·7; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). This ester was converted into the flavone through the corresponding diketone which was cyclised in the crude state. The resulting 3′ : 4′-*dimethoxy-6-methylflavone* crystallised from ligroin–chloroform (charcoal) in needles, m. p. 190° (Found: C, 72·5; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·3%). It showed a bright green fluorescence in sulphuric acid solution.

6-Methyl-3′ : 4′-methylenedioxyflavone (5). *5-Methyl-2-piperonyloyloxyacetophenone* formed plates, m. p. 118—120° (Found: C, 68·6; H, 4·9. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). *5-Methylsalicyloylpiperonyloylmethane*, obtained from the ester with potassium hydroxide in pyridine, separated in plates, m. p. 103° (Found: C, 68·3; H, 4·5%). *6-Methyl-3′ : 4′-methylenedioxyflavone* crystallised in needles, m. p. 218—220° (Found: C, 72·3; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). The fluorescence in sulphuric acid was light blue.

7 : 4′-Dimethoxyflavone (6). *2-p-Anisoyloxy-4-methoxyacetophenone* separated from methanol in needles, m. p. 84° (Found: C, 67·8; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), and gave by application of the Baker–Venkataraman reaction *p-anisoyl-4-methoxysalicyloylmethane* (Found: C, 68·0; H, 5·4%). This compound, which formed yellow needles, m. p. 108—110°, yielded on cyclisation the flavone, which separated from methanol in needles, m. p. 144—146° (Found: C, 72·3; H, 5·2. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%); Tambor (*Ber.*, 1916, **49**, 1710) gives m. p. 143—144°; Anand and Venkataraman (*Proc. Indian Acad. Sci.*, 1947, **26***A*, 284) give m. p. 149—150°.

4′-Methoxy-5 : 6-benzoflavone (10). The authentic sample of this flavone was prepared as described by Menon and Venkataraman (*J.*, 1931, 2594), who give m. p. 165°. It has now been found to be dimorphic with m. p.s 165° and 171—173° (Found: C, 79·9; H, 4·9. Calc. for $C_{20}H_{14}O_3$: C, 79·5; H, 4·6%).

3′ : 4′-Methylenedioxy-5 : 6-benzoflavone (11). This compound was prepared by Menon and Venkataraman's method (*loc. cit.*, p. 2596).

Preparation of Flavones from Benzylidenecoumaranones.—The corresponding flavones were obtained from benzylidenecoumaranones Nos. 1, 3, 4, 5, 6, 10, and 11 (but not from 2, 7, 8, 9, and 12) by refluxing a mixture of the benzylidenecoumaranone (1 part) and potassium cyanide (1 part) in ethanol for 2—6 hr. The product was cooled, diluted with water, and acidified. The precipitate was crystallised and the purified material (yield over 50%) compared with an authentic sample of the flavone (see above) by the mixed-m. p. method.

Other Experiments.—No useful result was obtained when 2-*p*-methoxybenzylidenecoumaran-3-one was heated with dry pyridine, methanolic sodium methoxide, or ethanolic potassium acetate. Similar negative results were obtained when the same benzylidenecoumaranone in dry pyridine was refluxed with sodium hydride, potassium hydroxide, sodium methoxide, sodium phenoxide, potassium carbonate, or potassium cyanide.

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A New Synthesis of Flavonols.

By J. E. GOWAN, P. M. HAYDEN, and T. S. WHEELER.

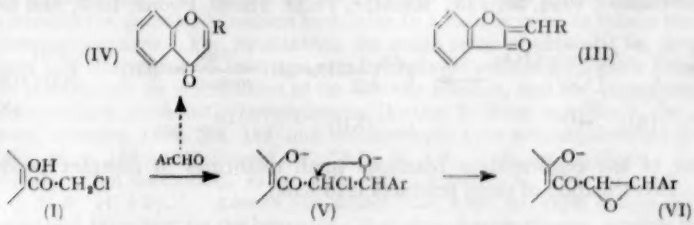
[Reprint Order No. 5887.]

Flavonols (II) are obtained in yields of up to 35% by the condensation of ω-chloro-*o*-hydroxyacetophenones (I) with aromatic aldehydes in the cold in presence of ethanolic alkali.

KOSTANECKI and his collaborators (Woker, Kostanecki, and Tambor, *Ber.*, 1903, **36**, 4235; Kostanecki, *Bull. Soc. chim. France*, 1903, **29**, Appendix, 1) showed that Friedländer (*e.g.*, Brüll and Friedländer, *Ber.*, 1897, **30**, 297; Simonis, *Z. angew. Chem.*, 1926, **39**, 1461) had obtained 2-arylidenecoumaran-3-ones (III) and not, as he thought, flavones (IV), by the reaction of ω-halogeno-*o*-hydroxyacetophenones (I) with aromatic aldehydes in presence of alkali. It has now been found, unexpectedly,* that if the condensation is carried out in the cold in presence of excess of alkali, the corresponding flavonol (II) is generally obtained in a yield of up to 35% calculated on (I). Twelve flavonols have been prepared in this way (Experimental, section A). With increase in temperature or a deficiency in alkali

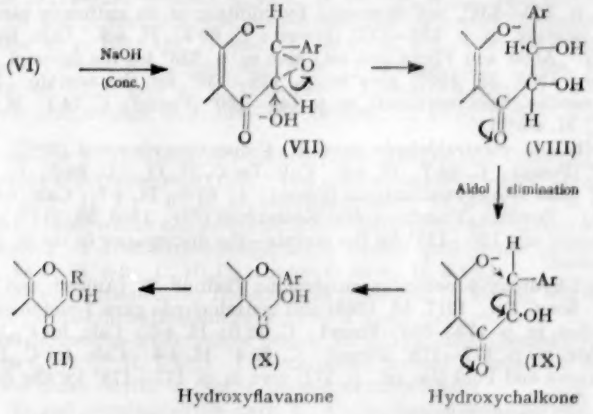
* See Hayden, O'Sullivan, Philbin, and Wheeler (*Research*, 1952, **5**, 396); the first observation was made by O'Sullivan (M.Sc. Thesis, National University of Ireland, 1951) in other work on derivatives of ω-chloro-*o*-hydroxyacetophenones (Philbin, O'Sullivan, and Wheeler, *J.*, 1954, 4174).

2-arylidenecoumaran-3-ones (III), hitherto the only known products, are obtained [Experimental, sections B and C; see also A (13)]. 3-Hydroxyflavanones (X) have also been isolated and are probably intermediate in the production of (II) (Experimental, section C).



The mechanism suggested for the production of (II) and (III) from (I) is based on the formation of the intermediate keto-epoxide (VI) (cf. Widman, *Ber.*, 1916, **49**, 477). The conversion of (VI) into (II) and (III) in the presence of alkaline hydrogen peroxide has been discussed by Geissman and Fukushima (*J. Amer. Chem. Soc.*, 1948, **70**, 1686; cf. Anand, Iyer, and Venkataraman, *Proc. Indian Acad. Sci.*, 1949, **29**, *A*, 203; Gripenberg, *Acta Chem. Scand.*, 1953, **7**, 1323). In the present instance the transformation of (VI) into (X) in excess of alkali is considered in view of the high concentration of OH^- to involve the external S_N2 reaction (VII ⟶ VIII) (see Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, Ltd., London, 1953, p. 341). This is followed by an aldol elimination of water (VIII ⟶ IX) and a chalkone–flavanone rearrangement (IX ⟶ X). The reactivity of epoxychalkones is such that alternative reaction mechanisms are possible.

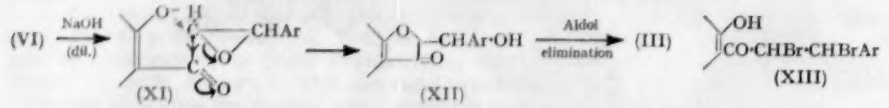
Geissman (personal communication) has suggested that the oxidation of (X) to (II) is effected by a portion of the epoxide (VI). As an alternative, Marathe, Chandorkar, and Limaye (*Rasāyanam*, 1952, **2**, 48; cf. Gripenberg, *loc. cit.*) have shown that 3-hydroxyflavanones (X) disproportionate in alkali in the absence of oxygen to form flavonols among other products; the reduced product is the corresponding flavanone (Marathe, *Science and Culture*, 1954, **19**, 516). When the amount of alkali present is reduced, the internal S_N2 reaction (XI ⟶ XII) predominates, and (XII) forms (III) by an aldol elimination. It



will be observed that compound (XII) is a probable intermediate in the synthesis of (III) by the condensation of an aromatic aldehyde with a coumaran-3-one (Gripenberg, *loc. cit.*).

Hayden, O'Sullivan, Philbin, and Wheeler (*Research*, 1952, **5**, 396) suggested that the new synthesis of (II) from (I) is analogous to the Rasoda reaction (Limaye, *Rasāyanam*,

1950, **2**, 1) for the production of flavonols by the action of water on 2′-hydroxychalkone dibromides (XIII) followed by treatment of the product (V; Cl replaced by Br) with alkali. The reaction scheme here discussed is similar to that established by Limaye and his collaborators for the Rasoda reaction (see Marathey, Ph.D. Thesis, Poona, 1952; *Science and Culture*, 1954, **20**, 135; Marathe, Ph.D. Thesis, Poona, 1953, and *loc. cit.*).



In some of the condensation reactions small quantities of complex products were obtained. Investigation of these products is in hand.

Experimental

Crystallisation was from ethanol unless otherwise stated.

(A) *Synthesis of Flavonols: Use of Excess of Cold Ethanolic Alkali.*—A mixture of the ω-chloro-2-hydroxyacetophenone (1 mol.; 1 pt.) and the aldehyde (2 mols.) in ethanol (5 pts.) was treated at below room temperature (ice-water cooling) with aqueous sodium hydroxide (50%; 3·5 mols. of NaOH) in ethanol (4 pts.). The precipitate of the sodium salt of the flavonol was collected after 3 hr. and decomposed by 10% hydrochloric acid to give the substantially pure flavonol (m. p. *ca.* 3° low). The pure product was obtained after one crystallisation, with a loss in yield of about 8%. No change in yield was obtained by increasing the proportion of aldehyde or alkali, or by carrying out the reaction in nitrogen or in presence of a trace of quinol. Addition of the ketone–aldehyde mixture to the ethanolic alkali reduced the yield. The following 12 flavonols were prepared in this way. The yield shown is of pure product (one crystallisation) calculated on the chloro-ketone.

(1) ω-Chloro-2-hydroxyacetophenone (ketone 1) (Fries and Pfaffendorf, *Ber.*, 1910, **43**, 212; Auwers, *Ber.*, 1926, **59**, 2899) and benzaldehyde gave flavonol (30%), pale yellow needles, m. p. 169—170°, not depressed by addition of an authentic sample (Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, **42**, *B*, 5) [acetate, m. p. 109° (Found: C, 72·4; H, 4·6. Calc. for $C_{17}H_{12}O_4$: C, 72·9; H, 4·3%)]. Kostanecki and Szabrański (*Ber.*, 1904, **37**, 2820) give m. p. 169—170° for the flavonol and 110—111° for the acetate. *3-Benzoyloxyflavone* formed needles (from methanol), m. p. 159—160° (Found: C, 77·1; H, 4·3. $C_{22}H_{14}O_4$ requires C, 77·2; H, 4·1%).

(2) Ketone (1) and *p*-anisaldehyde gave 4′-methoxyflavonol (31%), yellow prisms (from chloroform), m. p. 233—234°, not depressed by addition of an authentic sample (Algar and Flynn, *loc. cit.*) [acetate, m. p. 132—133° (Found: C, 69·5; H, 4·8. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·6%)]. Algar and Flynn (*loc. cit.*) give m. p. 235° for the flavonol. Edelstein and Kostanecki (*Ber.*, 1905, **38**, 1507) give m. p. 138—139° for the acetate. *3-Benzoyloxy-4′-methoxyflavone*, needles (from methanol), m. p. 149—150° (Found: C, 74·1; H, 4·4. $C_{23}H_{16}O_5$ requires C, 74·2; H, 4·3%).

(3) Ketone (1) and veratraldehyde gave 3′: 4′-dimethoxyflavonol (30%), yellow needles, m. p. 201—202° (Found: C, 68·7; H, 4·9. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7%) [acetate, m. p. 112—113° after two crystallisations (Found: C, 67·0; H, 4·7. Calc. for $C_{19}H_{16}O_6$: C, 67·0; H, 4·7%)]. Berstein, Fraschina, and Kostanecki (*Ber.*, 1905, **38**, 2177) give m. p. 199—200° for the flavonol and 130—131° for the acetate—the discrepancy in the m. p. of the acetate cannot be explained.

(4) ω-Chloro-2-hydroxy-4-methoxyacetophenone (ketone 2) (Auwers and Pohl, *Annalen*, 1914, **405**, 264; Sonn, *Ber.*, 1917, **50**, 1268) and benzaldehyde gave 7-methoxyflavonol (33%), pale yellow needles, m. p. 179—180° (Found: C, 72·0; H, 4·5. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) [acetate, m. p. 177—178° (Found: C, 69·4; H, 4·4. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5%)]. Auwers and Pohl (*loc. cit.*, p. 271) give m. p. 177—178° for the flavonol and 176° for the acetate.

(5) Ketone (2) and *p*-anisaldehyde gave 7: 4′-dimethoxyflavonol (13%), yellow needles, m. p. 192—193° (Found: C, 68·4; H, 4·7. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7%) [acetate, m. p. 193° (Found: C, 66·8; H, 4·9. Calc. for $C_{19}H_{16}O_6$: C, 67·1; H, 4·8%)]. Juppen and Kostanecki (*Ber.*, 1904, **37**, 4162) give m. p. 196—197° for the flavonol and 193—194° for the acetate.

(6) Ketone (2) and veratraldehyde gave 7 : 3′ : 4′-trimethoxyflavonol (fisetin 7 : 3′ : 4′-trimethyl ether) (20%), yellow needles, m. p. 186—187° (Found : C, 66·2; H, 5·0. Calc. for $C_{18}H_{16}O_6$: C, 65·9; H, 4·9%) [acetate, m. p. 169—170° (Found : C, 64·9; H, 5·0. Calc. for $C_{20}H_{18}O_7$: C, 64·9; H, 4·9%)]. Kostanecki and Nitkowski (*Ber.*, 1905, **38**, 3588) give m. p. 186° for the flavonol and 170° for the acetate. It was necessary in the preparation of this flavonol to increase the quantity of sodium hydroxide to 5 mols. in order to reduce the formation of benzylidenecoumaranone. For purification, the crude material obtained by decomposition of the sodium salt was extracted from benzene by aqueous sodium hydroxide (2%), and the flavonol was precipitated by acidification of the alkaline solution, and was crystallised.

(7) ω-Chloro-2-hydroxy-5-methylacetophenone (ketone 3) (Fries and Finck, *Ber.*, 1908, **41**, 4276; Auwers, *Annalen*, 1909, **364**, 164) and benzaldehyde gave 6-methylflavonol (33%), light brown needles, m. p. 198—199° (Found : C, 76·1; H, 4·8. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%) [benzoate (from methanol), m. p. 168—169° (Found : C, 77·3; H, 4·7. Calc. for $C_{23}H_{16}O_4$: C, 77·5; H, 4·5%)]. Auwers and Müller (*Ber.*, 1908, **41**, 4239) give m. p. 196—197° for the flavonol and 167—168° for the benzoate. *3-Acetoxy-6-methylflavone*, needles, m. p. 109—110° (Found : C, 73·9; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

(8) Ketone (3) and *o*-anisaldehyde gave little precipitate of the sodium salt of the flavonol by the standard procedure. The solution was filtered and acidified with 10% hydrochloric acid, and, next day, the precipitate of *2′-methoxy-6-methylflavonol* (24%) was collected. It formed prisms, m. p. 201—202° (from aqueous methanol followed by chloroform–ligroin) (Found : C, 72·7; H, 5·2. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). The ethanolic ferric colour was purple, and the fluorescence in sulphuric acid blue. *3-Acetoxy-2′-methoxy-6-methylflavone* separated as a powder, m. p. 156—157° (Found : C, 70·8; H, 5·3. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%).

In a preliminary experiment under the conditions described at (A) above, but without cooling, ketone (3) and *o*-anisaldehyde gave a precipitate of 2-o-*anisylidene-5-methylcoumaran-3-one* (3%), yellow powder (Found : C, 76·5; H, 5·2. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%), m. p. 187—188° (from aqueous ethanol), not depressed by addition of a sample, m. p. 189—190°, prepared by the general method of Auwers and Müller (*loc. cit.*) from *o*-anisaldehyde and 5-methylcoumaran-3-one. This compound gave a red solution in sulphuric acid which did not fluoresce in ultra-violet light. The isomeric 2′-methoxy-6-methylflavone has m. p. 110° (Baker and Besly, *J.*, 1940, 1106).

(9) Ketone (3) and *p*-anisaldehyde gave 4′-methoxy-6-methylflavonol (35%), yellow needles, m. p. 192—193° (Found : C, 72·0; H, 4·9; OMe, 11·6. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0; 1OMe, 11·0%) [acetate, m. p. 137—138° (Found : C, 70·9; H, 5·0; OMe, 9·6. Calc. for $C_{19}H_{16}O_5$: C, 70·4; H, 5·0; 1OMe, 9·6%)]. Limaye (*Rasāyanam*, 1950, **2**, 5) gives m. p. 191—192° for the flavonol and 136—137° for the acetate. *3-Benzoyloxy-4′-methoxy-6-methylflavone* formed needles, m. p. 171—172° (Found : C, 74·1; H, 4·7. $C_{24}H_{18}O_5$ requires C, 74·6; H, 4·7%).

(10) Ketone (3) and piperonaldehyde gave 6-methyl-3′ : 4′-methylenedioxyflavonol (25%), pale yellow needles, m. p. 196—197° (Found : C, 68·8; H, 4·2. Calc. for $C_{17}H_{12}O_5$: C, 68·9; H, 4·1%). Ozawa, Okuda, Kawanishi, and Fujii (*J. Pharm. Soc. Japan*, 1951, **71**, 1178; *Chem. Abs.*, 1952, **46**, 6124) give m. p. 195—196°. *3-Acetoxy-6-methyl-3′ : 4′-methylenedioxyflavone* formed pale pink needles, m. p. 168—169° (Found : C, 67·3; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%).

(11) Ketone (3) and 2 : 4-dimethoxybenzaldehyde (Cullinane and Philpott, *J.*, 1929, 1763) gave 2′ : 4′-*dimethoxy-6-methylflavonol* (18%; two crystallisations), yellow prisms, m. p. 230—231° (Found : C, 69·2; H, 5·1. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). The flavonol gave a dark green ethanolic ferric colour and exhibited a blue ultra-violet fluorescence in sulphuric acid solution. *3-Acetoxy-2′ : 4′-dimethoxy-6-methylflavone* formed pale yellow prisms, m. p. 134—135° (Found : C, 68·3; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

In a preliminary experiment under the standard conditions (A above), but without cooling, ketone (3) and 2 : 4-dimethoxybenzaldehyde gave a small precipitate of *2-(2 : 4-dimethoxybenzylidene)-5-methylcoumaran-3-one*, yellow prisms, m. p. 192—193° (Found : C, 73·2; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%) The compound formed in sulphuric acid a red non-fluorescent solution characteristic of 2-benzylidenecoumaran-3-ones.

(12) Ketone (3) and veratraldehyde gave 3′ : 4′-*dimethoxy-6-methylflavonol* (33%), yellow needles (from aqueous ethanol), m. p. 200—201° (Found : C, 69·1; H, 5·2. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). The ethanolic ferric colour was violet and the ultra-violet fluorescence in sulphuric acid solution was yellow. *3-Acetoxy-3′ : 4′-dimethoxy-6-methylflavone* formed needles, m. p. 146—147° (Found : C, 68·2; H, 5·3. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

(13) Ketone (3) and *p*-hydroxybenzaldehyde gave only a trace of precipitate when mixed

with ethanolic alkali as described at (A) above. The solution was filtered and acidified with concentrated hydrochloric acid. Next day the precipitate of 2-*p*-hydroxybenzylidene-5-methylcoumaran-3-one was collected and crystallised from aqueous acetic acid. It formed an orange powder (18%), m. p. 252—254° (decomp.). Auwers and Müller (*Ber.*, 1908, **41**, 4238) give m. p. 254—255°. Methylation of the coumaranone by methyl sulphate and potassium carbonate in acetone gave 2-*p*-anisylidene-5-methylcoumaran-3-one, yellow needles (from methanol), m. p. 153—154°, not depressed by addition of a sample prepared by Auwers and Müller's method (*loc. cit.*) from *p*-anisaldehyde and 5-methylcoumaran-3-one (cf. Auwers and Anschütz, *Ber.*, 1921, **54**, 1556).

(B) *Production of Benzylidenecoumaranones: Use of Excess of Hot Ethanolic Alkali.*—The following 2-benzylidenecoumaran-3-ones were precipitated when ketone (2) and the corresponding aldehyde were mixed with concentrated ethanolic alkali as described at (A), but at about 70°. Yields calculated on the chlorohydroxy-ketone are given in parentheses.

2-Benzylidene-6-methoxycoumaran-3-one separated in needles (50%), m. p. 145—146° (Found: C, 75·8; H, 4·6. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%). Auwers and Pohl (*Annalen*, 1914, **405**, 268) give the same m. p. The isomeric 7-methoxyflavone has m. p. 110—111° (Emilewicz and Kostanecki, *Ber.*, 1899, **32**, 312).

2-*p*-Anisylidene-6-methoxycoumaran-3-one crystallised in yellow needles (60%), m. p. 134—135° (Found: C, 72·4; H, 5·3. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%). Panse, Shah, and Wheeler (*J. Univ. Bombay*, 1941, **10**, 83) give m. p. 134°. The isomeric 7 : 4′-dimethoxyflavone has m. p. 143—144° (Tambor, *Ber.*, 1916, **49**, 1710).

Methoxy-2-veratrylidene-6-coumaran-3-one formed pale yellow needles (70%), m. p. 185—186° (Found: C, 69·7; H, 5·4. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·1%). Auwers and Pohl (*loc. cit.*) give m. p. 183—184°. The solution in sulphuric acid was deep red with a weak orange-red fluorescence. The isomeric 7 : 3′ :4′-trimethoxyflavone had m. p. 177° (Dr. A. Schiavello, personal communication; cf. Schiavello and Sebastiani, *Gazzetta*, 1949, **79**, 912).

(C) *Production of 3-Hydroxyflavanones and of 2-Benzylidenecoumaran-3-ones: Use of Less than 0·5 Mol. of Sodium Hydroxide.*—A mixture of chlorohydroxy-ketone (1 mol.; 1 pt.), aldehyde (1·5 mol.), aqueous sodium hydroxide (5%; 0·35 mol. of NaOH), and ethanol (10 pts.) was shaken for 3 hr. and, next day, was diluted with water (75 pts.) and extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite, aqueous sodium hydroxide (4%), and water, and dried. The residue obtained on evaporation of the solvent was crystallised. The yields shown are calculated on sodium hydroxide which was in deficit.

3-Hydroxyflavanones. Ketone (1) and benzaldehyde gave 3-hydroxyflavanone (20%), prisms, m. p. 175—177°, raised by crystallisation from methanol to 182—183° (Found: C, 75·3; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%). The product did not depress the m. p. of an authentic sample (Reichel and Steudel, *Annalen*, 1942, **553**, 90). Oyamada (*Bull. Chem. Soc. Japan*, 1941, **16**, 411; *Chem. Abs.*, 1947, **41**, 3797) gives m. p. 183—184° for the hydroxyflavanone.

Ketone (1) and veratraldehyde gave 3-hydroxy-3′ : 4′-dimethoxyflavanone (3%), needles (from methanol), m. p. 157—158° (Found: C, 68·4; H, 5·4. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·4%). Oyamada (*J. Chem. Soc. Japan*, 1943, **64**, 335; *Chem. Abs.*, 1947, **41**, 3798) gave m. p. 155—157°.

2-Benzylidenecoumaran-3-ones. Ketone (1) and *p*-anisaldehyde gave 2-*p*-anisylidenecoumaran-3-one (11%), yellow needles, m. p. 138—139°, not depressed by addition of a sample prepared from the corresponding coumaranone and aldehyde (cf. Auwers and Anschütz, *Ber.*, 1921, **54**, 1558, 3331) (Found: C, 76·6; H, 5·1. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%).

Ketone (3) and benzaldehyde gave 2-benzylidene-5-methylcoumaran-3-one (40%), pale yellow prisms (from methanol), m. p. 119°, not depressed by addition of an authentic sample (Auwers and Müller, *Ber.*, 1908, **41**, 4238) (Found: C, 81·9; H, 5·2. Calc. for $C_{16}H_{12}O_2$: C, 81·3; H, 5·1%).

Ketone (3) and *p*-anisaldehyde gave 2-*p*-anisylidene-5-methylcoumaran-3-one (30%), yellow needles (from methanol), m. p. 152—153°, not depressed by addition of an authentic sample (Auwers and Anschütz, *loc. cit.*, p. 1556).

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α-1 : 4-*Glucosans. Part III.* The Molecular Structure of Brewer's Yeast Glycogen.*

By D. J. Manners and Khin Maung.

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Brewer's yeast (*Saccharomyces cerevisiae*) contains a glucosan which is stained reddish-brown by iodine, is degraded by salivary α-amylase, and has a molecular weight of $\sim 2 \times 10^6$. The polysaccharide has an average chain length of 13, a β-amylolysis limit of 44%, and a phosphorolysis limit of 23%. The molecular structure therefore resembles that of a typical glycogen. The properties of the glycogens from baker's yeast and brewer's yeast are compared.

Although the glycogen from baker's yeast has been studied several times (*e.g.*, Northcote, *Biochem. J.*, 1953, **53**, 348; Jeanloz, *Helv. Chim. Acta*, 1944, **27**, 1501), little attention has been paid to the corresponding polysaccharide from brewer's yeast. A sample of the latter, isolated by Daoud and Ling (*J. Soc. Chem. Ind.*, 1931, **50**, 365T), had $[\alpha]_D$ +179° in water and was stained brownish-red by iodine; Yokoyama (*Beitr. Physiol.*, 1925, **3**, 95) found $[\alpha]_D$ +192° in water. No structural examination appears to have been published. The present communication deals with an investigation of the molecular structure of brewer's yeast glycogen; this is being used as a substrate in studies on the carbohydrate-metabolising enzymes in this organism.

The glycogen was extracted from yeast cell-wall material (obtained by disruption of the whole yeast with hot dilute sodium hydroxide) with 0·5N acetic acid (Bell and Northcote, *J.*, 1950, 1944; Northcote and Horne, *Biochem. J.*, 1952, **51**, 232), and was purified by several precipitations with 80% acetic acid (cf. Bell and Young, *Biochem. J.*, 1934, **28**, 882) and with ethanol. The purified glycogen gave an opalescent solution in water ($[\alpha]_D$ +198°), which was stained reddish-brown by iodine. The iodine binding power of the glycogen was quantitatively determined by Mr. D. M. W. Anderson, using the potentiometric titration method described by Anderson and Greenwood (*Chem. and Ind.*, 1953, 642); it was similar to that of mammalian glycogens. Acid hydrolysis of the glycogen gave glucose (96%) and no other reducing sugar. The glycogen was readily attacked by salivary α-amylase, as shown by the rapid loss of iodine staining power, and the production of glucose, maltose, and α-dextrins; the glucosidic linkages in the glycogen are therefore predominantly of the α-1 : 4 type. Since maltulose was absent from the α-amylolytic digest, fructose is not a constituent of the glycogen (cf. Peat, Roberts, and Whelan, *Biochem. J.*, 1952, **51**, xvii). Oxidation of the glycogen by potassium periodate (cf. Halsall, Hirst, and Jones, *J.*, 1947, 1399; Bell and Manners, *J.*, 1952, 3641) and determination of the maximum amount of formic acid produced indicated a unit-chain length of thirteen glucose residues. In an attempt to detect 1 : 2 or 1 : 3 linkages, periodate-oxidised glycogen was hydrolysed with acid, and the hydrolysate analysed for glucose (cf. Hirst, Jones, and Roudier, *J.*, 1948, 1779; Bell and Manners, *J.*, 1954, 1891). Paper chromatography showed that glucose was absent; the glycogen must therefore contain only α-1 : 4 and 1 : 6 glucosidic linkages. Treatment of the glycogen with β-amylase gave 44% conversion into maltose, indicating that the exterior chains comprise 8 glucose residues; the interior chains, on the average, thus contain 4 glucose residues. Treatment of the glycogen with muscle phosphorylase in the presence of excess of inorganic phosphate resulted in a 23% conversion into glucose 1-phosphate; 12-unit and 13-unit glycogens from various animal tissues have phosphorolysis limits of 20—25% (Liddle and Manners, unpublished). Examination of the glycogen in an ultracentrifuge, by Dr. C. T. Greenwood, showed it to be multimolecular, the sedimentation constant (S_{20}) being 52×10^{-13} c.g.s. units [equivalent to a molecular weight of *ca.* 2×10^6, the diffusion constant being assumed to be of the same order as that of other glycogens (cf. Bell, Gutfreund, Cecil, and Ogston,

* Part II, *J.*, 1954, 3527.

Biochem. J., 1948, **42**, 405)]. An estimate of the shape of the molecule, and the degree of multiple branching in the molecule will be described in a later communication.

The available data indicate that brewer's yeast glycogen consists of *ca.* 10^3 unit-chains, each comprising, on the average, 13 α-1 : 4-linked glucose residues, and randomly interlinked by 1 : 6-glucosidic linkages. The molecular structure thus resembles that of the majority of the glycogens from mammalian, invertebrate, and protozoan tissues examined in our previous studies (Bell and Manners, *loc. cit.*; Manners and Ryley, *Biochem. J.*, 1952, **52**, 480); nevertheless, small but significant differences in degree and position of branching between the baker's yeast and the brewer's yeast glycogen are revealed (see Table).

A comparison of the properties of yeast glycogens with rabbit-liver glycogen.

Source :	Baker's yeast		Brewer's yeast	Rabbit-liver
	A	*B*		*C*
$[\alpha]_D$ in water	+184°	+187°	+198°	+196°
Unit-chain length	11—12	—	13	12—13
β-Amylolysis limit	50	46—48·5	44	43
Exterior chain length *	8	—	8	8
Interior chain length †	2—3	—	4	3—4

A, Data from Northcote (*loc. cit.*). *B*, Data from Jeanloz (*loc. cit.*). *C*, Data from Bell and Manners (*loc. cit.*).

* No. of glucose units removed on β-amylolysis plus 2·5. † Unit-chain length − Exterior chain length − 1.

In our previous papers (Bell and Manners, *loc. cit.*; Manners and Ryley, *loc. cit.*) exterior chain lengths were calculated on the assumption that the exterior "stubs" of β-limit dextrins contained 1·5 glucose residues (cf. Meyer, *Adv. Enzymology*, 1943, **3**, 109); Peat, Whelan, and Thomas (*J.*, 1952, 4546), however, have shown that a proportion of the "stubs" in a β-dextrin from waxy-maize starch contain two or three glucose residues. A mean of these latter figures has been used in the present calculation.

In view of the different conditions of growth and fermenting properties of baker's and brewer's yeast, and hence, enzymatic composition, it is not unexpected that the glycogens show small differences in molecular structure; the unit-chain length and the position of branching in the chains depend upon the "balance" between the activities of phosphorylase and the branching and debranching enzymes, *i.e.*, on the metabolic condition of the organism at the time of isolation of the glycogen.

Experimental

Analytical Methods.—(a) *Determination of reducing sugar.* Reducing sugars were determined by use of the Shaffer–Somogyi reagent 60 (*J. Biol. Chem.*, 1933, **100**, 695) as modified by Hanes and Cattle (*Proc. Roy. Soc.*, 1938, *B*, **125**, 387) or by the Somogyi reagent (*J. Biol. Chem.*, 1945, **160**, 61) which had been calibrated against glucose and maltose.

(b) *Paper chromatography.* Descending chromatograms were carried out at room temperature with Whatman No. 1 paper and benzene–pyridine–butanol–water (1 : 3 : 5 : 3) as solvent. Development was by spraying with aniline oxalate or with a silver nitrate–sodium hydroxide reagent (Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444).

(c) *Iodine stain.* Polysaccharide solution (2 ml.) was added to iodine solution (1 ml.; containing 1 mg. of iodine and 10 mg. of potassium iodide per ml.) and water (2 ml.), and the absorption value of the polysaccharide–iodine complex measured on a Spekker Photoelectric Absorptiometer (1 cm. cells), an Ilford filter No. 603 being used, against an iodine blank.

(d) *Determination of glucose 1-phosphate.* Glucose 1-phosphate was determined by a slight modification of Allen's method (*Biochem. J.*, 1940, **34**, 858).

Preparation of Glycogen.—A dispersion of washed brewer's yeast (1·5 kg.) in 3% sodium hydroxide (1 l.) was heated at 95° for 6 hr. (cf. Northcote and Horne, *loc. cit.*). After the mixture had cooled, the cell-wall material was collected on the centrifuge and treated again with hot 3% sodium hydroxide. (The sodium hydroxide extracts did not contain any appreciable amount of glycogen.) The cell-wall material was extracted by three successive treatments with 0·5N-acetic acid (each 500 ml.) at 75° for 2 hr. The combined acetic acid extracts were concentrated under reduced pressure to about 500 ml., and ethanol (6 vols.) was added. The

crude precipitate of glycogen was purified by three precipitations from 80% acetic acid (Bell and Young, *loc. cit.*) and finally from ethanol. The yield was 17·7 g.

Properties of the Glycogen.—The glycogen had $[\alpha]_D^{18}$ +198° (*c*, 0·25 in H_2O); +175° (*ca.* 0·50 in N-NaOH) (Found: N, 0·05%; P, nil; Ash, 0·10%). An aqueous solution was opalescent, and was stained red-brown with iodine. Hydrolysis by 1·5N-sulphuric acid at 100° for 2 hr. gave glucose and no other sugar (paper chromatography). The glycogen had a glucose content of 96%, determined by quantitative acid hydrolysis (Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224).

Salivary α-Amylolysis of the Glycogen.—Salivary α-amylase solution was prepared by dissolving freeze-dried human saliva in distilled water, and removing insoluble material by centrifugation. The amylase solution showed no maltase activity, but was contaminated with maltotriase. During the digestion of waxy-maize starch, maltose, maltotriose, and α-dextrins were the initial products of the reaction, and glucose, maltose, and α-dextrins the end-products (cf. Whelan and Roberts, *Nature*, 1952, **170**, 748; *J.*, 1953, 1298).

An enzymic digest was set up containing glycogen (50·0 mg.), phosphate–citrate buffer (0·16M with respect to phosphate) of pH 7·0 (20 ml.), sodium chloride (25·0 mg.), salivary amylase solution (1 ml.), and water (29 ml.). Aliquot portions (2 ml.) were analysed at intervals (Shaffer–Somogyi reagent 60), after incubation at 35°.

The decrease in iodine-staining power was as follows:

Time of incubation (min.)	0	4	10	20
Absorption value	0·305	0·035	0·020	0·010

The apparent percentage conversion into maltose after 1, 2, and 48 hours' incubation was 62, 68, and 95, respectively.

Paper chromatography showed the presence of glucose ($R_G = 1$), maltose ($R_G = 0·55$), and a series of sugars of higher molecular weight ($R_G < 0·09$) in the digest. Maltulose was absent.

Potassium Periodate Oxidation of the Glycogen.—Glycogen (549·0 mg.) was dissolved in 5% potassium chloride solution (100 ml.); 10 ml. were withdrawn for a control determination. 8% (w/v) sodium metaperiodate (20 ml.) was added to the bulk, from which 10-ml. portions were withdrawn at intervals for determination of formic acid by titration in a carbon dioxide-free atmosphere against 0·01N-sodium hydroxide, methyl-red being used as indicator (cf. Halsall, Hirst, and Jones, *loc. cit.*; Bell and Manners, *loc. cit.*). The following results were obtained.

Time (hr.)	96	168	266	386
Total formic acid produced (mg.)	8·9	10·2	10·6	10·5
Apparent chain length * (glucose residues) ...	15·6	13·6	13·2	13·2

* Calculated from the weight of glycogen oxidised.

A 12-unit or 14-unit glycogen would yield 11·6 or 10·0 mg. of formic acid, respectively.

The remaining solution of periodate-oxidised glycogen was neutralised with ethylene glycol (5 ml.) and dialysed against running tap water for 36 hr., and the non-diffusible material collected by freeze-drying. 50 mg. of this were hydrolysed by 2N-sulphuric acid (2 ml.) at 100° for 3 hr. No glucose could be detected in the hydrolysate by paper chromatography; brewer's yeast glycogen does not therefore contain 1 : 2- or 1 : 3-glucosidic linkages.

β-*Amylolysis of the Glycogen.*—β-Amylase was prepared from soya beans by Bourne, Macey, and Peat's method (*J.*, 1945, 882). A solution of β-amylase was prepared by dissolving soya bean β-amylase (50 mg.) in 0·2M-acetate buffer (pH 4·6; 20 ml.), and removing insoluble material by centrifugation; the supernatant liquid had an activity of 125 units/ml., estimated by Hobson, Whelan, and Peat's method (*J.*, 1950, 3566). Control experiments with maltose and starch showed it to be free from maltase and α-amylase. Glycogen (48·4 mg.) was incubated with 0·2M-acetate buffer (pH 4·6; 6 ml.), water (21 ml.), and β-amylase solution (3 ml.; 375 units) at 37°. Samples (3 ml.) were withdrawn at intervals and analysed for maltose. The course of degradation was as follows:

Time of incubation (hr.)	1	2	20	44
% Conversion into maltose	30·7	38·4	43·5	44·0

In a duplicate experiment with 50·4 mg. of glycogen, the β-amylolysis limit was 43·8%.

Phosphorolysis of the Glycogen [with A. Margaret Liddle].—Glycogen (52·4 mg.) was incubated at 35° with 0·5M-phosphate buffer (pH 6·8; 2·0 ml.), adenylic acid (1 mg.), muscle

phosphorylase solution (0·20 ml.), and water to a total volume of 10 ml. Crystalline rabbit-muscle phosphorylase was prepared by Green and Cori's method (*J. Biol. Chem.*, 1943, **151**, 21).

Time of incubation (hr.)	5	24	48
% Conversion into glucose 1-phosphate	20·0	23·2	23·2

In a duplicate experiment with 53·4 mg. of glycogen, the phosphorolysis limit was 22·8%.

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12-*Oxygenated Pregnane Derivatives. Part V.** 12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione*.

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Conversion of hecogenin into 12β : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XI) is described.

Deoxycholic acid proved unsatisfactory for the preparation of the dione (XI) as conversion into 3α : 12β-dihydroxycholanic acid could not be achieved in adequate yield (cf. Koechlin and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 918). Better results followed the use of hecogenin (I; R = :O, R′ = H).

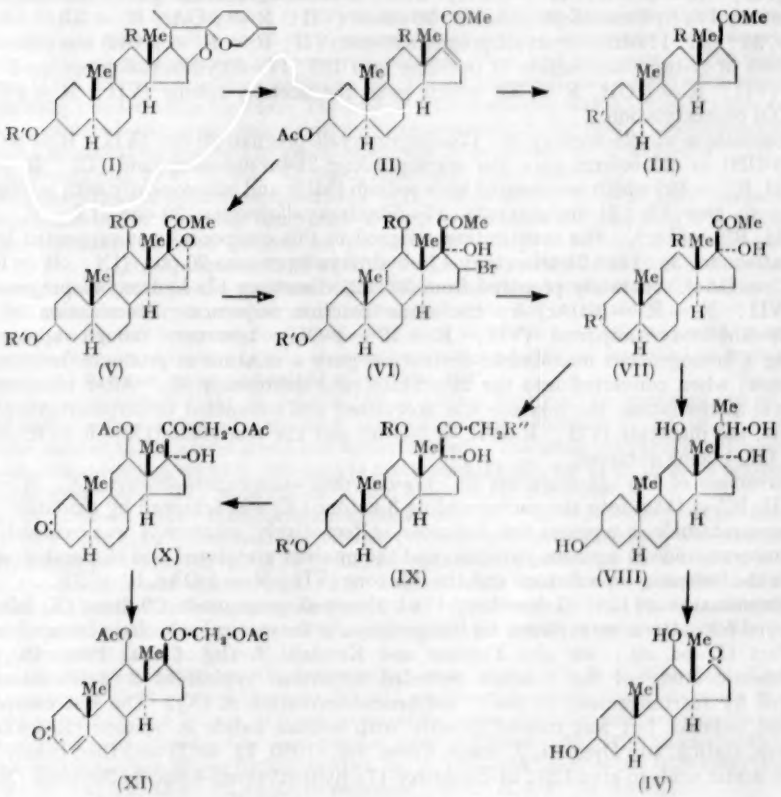
Reduction of hecogenin to 5α : 22a-spirostan-3β : 12β-diol (rockogenin) (I; R = β-OH, R′ = H) has previously been effected by hydrogen and Adams catalyst, with sodium in ethanol, or with lithium aluminium hydride (Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *J. Amer. Chem. Soc.*, 1947, **69**, 2167; Hirschmann, Snoddy, and Wendler, *ibid.*, 1952, **74**, 2693; Rothman, Wall, and Eddy, *ibid.*, p. 4013). We now find that sodium borohydride is preferable for this purpose. Acetylation of the product, followed by separation of the 12α- and the 12β-isomer and degradation, furnished 3β : 12β-diacetoxy*allo*pregn-16-en-20-one (II; R = β-OAc) (cf. U.S.P. 2,408,828), the structure of which was confirmed by hydrogenation, hydrolysis, and oxidation to *allo*-pregnane-3 : 12 : 20-trione.

An alternative route to the compound (II; R = β-OAc) was also examined. Hecogenin acetate was degraded to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = :O) (cf. Part II, *J.*, 1954, 2209). Reduction with lithium aluminium hydride gave a mixture of *allo*pregn-16-ene-3β : 12β : 20-triols which was directly oxidised with manganese dioxide in benzene, a specific oxidant for allylic alcohols (cf. Sondheimer, Amendolla, and Rosenkrantz, *J. Amer. Chem. Soc.*, 1953, **75**, 5930). Acetylation of the product, however, furnished 3β-acetoxy-12β-hydroxy*allo*pregn-16-en-20-one (II; R = β-OH) in place of the expected acetate (II; R = β-OAc). The structure of this product followed from its catalytic hydrogenation to 3β-acetoxy-12β-hydroxy*allo*pregnan-20-one (III; R = β-OH, R′ = β-OAc) which passed into (i) the known 3β-acetoxy*allo*pregnane-12 : 20-dione (III; R = :O, R = β-OH) on oxidation and (ii) the known *allo*pregnane-3 : 12 : 20-trione (III; R = R′ = :O) on hydrolysis and oxidation. Attempts to convert the monoacetate (II; R = β-OH) into the foregoing diacetate (II; R = β-OAc), however, proved unsuccessful. This surprising result is only partially explained by the known difficulty in acylating 12β-hydroxy-steroids (Marker *et al.*, *loc. cit.*; Pataki, Meyer, and Reichstein, *Helv. Chim. Acta*, 1953, **36**, 1295) as the 17α-hydroxy-derivatives described below passed easily into the 12β-acetates.

* Part IV, *J.*, 1954, 4688.

Conversion of the diacetate (II; R = β-OAc) into 3β : 12β-diacetoxy-17α-hydroxy*allo*pregnan-20-one (VII; R = R′ = β-OAc) followed the general methods described in Parts I (*J.*, 1954, 1825) and II (*loc. cit.*). The former compound was treated with alkaline hydrogen peroxide to give 3β : 12β-diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (V; R = R′ = Ac), which passed into 3β : 12β-diacetoxy-16β-bromo-17α-hydroxy*allo*pregnan-20-one (VI; R = R′ = Ac) on reaction with hydrogen bromide. Reductive removal of the bromine atom furnished the required (VII; R = R′ = β-OAc).

The constitution assigned to the last compound was established (i) by its dehydration with phosphorus oxychloride in pyridine to 3β : 12β-diacetyoxy*allo*pregn-16-en-20-one (II; R = β-OAc), (ii) by its hydrolysis with 2 molar equivalents of alkali to 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (VII; R = R′ = β-OH), also prepared from (II; R = β-OH) by the foregoing reaction sequence and converted into (VII; R = R′ = β-OAc) by acetic anhydride–pyridine at room temperature, and (iii) by its reduction [or that of (VII; R = R′ = β-OH)] with sodium borohydride in the presence of excess of sodium hydrogen



carbonate to *allo*pregnane-3β : 12β : 17α : 20ξ-tetrol (VIII), which was oxidised with sodium bismuthate in acetic acid to a product formulated as 3β : 12β-dihydroxyandrostan-17-one (IV) and different from the isomeric 3β : 12α-dihydroxyandrostan-17-one described in Part II (*loc. cit.*).

Conversion of the diacetate (VII; R = R′ = β-OAc) into 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (VII; R = β-OAc, R′ = β-OH) could not be effected by methanolic sodium hydrogen carbonate at room temperature or by 1 equivalent of sodium

carbonate in methanol, complete hydrolysis to the triol (VII; R = R′ = β-OH) taking place (cf. the behaviour of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one described in Part I, *loc. cit.*). Hydrolysis with catalytic quantities of hydrochloric acid in methanolic solution for 3 hours on the steam-bath, however, furnished the diol (VII; R = β-OAc, R′ = β-OH). The last compound was additionally prepared from 3β : 12β-diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (V; R = R′ = Ac). Partial hydrolysis with 1 equivalent of methanolic potassium carbonate at room temperature gave 12β-acetoxy-16α : 17α-epoxy-3β-hydroxy*allo*pregnan-20-one (V; R = Ac, R′ = H) [cf. the behaviour of (VII; R = R′ = β-OAc), above], which was converted into the bromohydrin (VI; R = Ac, R′ = H) by hydrogen bromide in chloroform solution. Use of acetic acid as solvent led to reacetylation of the 3β-hydroxyl group. Debromination with hydrogen and palladium–calcium carbonate gave the diol (VII; R = β-OAc, R′ = β-OH).

Before proceeding to the introduction of the 21-acetoxyl group into the last compound, the conversion of the 3β-hydroxyl group into carbonyl was examined. Oxidation of the diol (VII; R = β-OAc, R′ = β-OH) with *N*-bromoacetamide gave the expected 12β-acetoxy-17α-hydroxy*allo*pregnane-3 : 20-dione (VII; R = β-OAc, R′ = :O). Alternatively, 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (VII; R = R′ = β-OH) was converted by excess of *N*-bromoacetamide in pyridine into 12β : 17α-dihydroxy*allo*pregnane-3 : 20-dione (VII; R = β-OH, R′ = :O) which gave the acetoxy-ketone (VII; R = β-OAc, R′ = :O) on acetylation.

Bromination of 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (VII; R = β-OAc, R′ = β-OH) in chloroform gave the corresponding 21-bromo-compound (IX; R = Ac, R′ = H, R″ = Br) which was treated with sodium iodide and subsequently with potassium acetate to give 12β : 21-diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (IX; R = Ac, R′ = H, R″ = OAc). The constitution assigned to this compound was supported by its acetylation to 3β : 12β : 21-triacetoxy-17α-hydroxy*allo*pregnan-20-one (IX; R = R′ = Ac, R″ = OAc), separately prepared from 3β : 12β-diacetoxy-17α-hydroxy*allo*pregnan-20-one (VII; R = R′ = β-OAc) by the same reaction sequence. Bromination of the 3β : 12β-dihydroxy-compound (VII; R = R′ = β-OH), however, though apparently yielding a homogeneous monobromo-derivative, gave a mixture of products (mixture *A*, see below) when converted into the 21-acetate (and debrominated). After unsuccessful attempts at resolution, the mixture was acetylated and submitted to chromatography on alumina, the diacetate (VII; R = R′ = β-OAc) and the triacetate (IX; R = R′ = Ac, R″ = OAc) being obtained.

Conversion of 12β : 21-diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (IX; R = Ac, R′ = H, R″ = OAc) into the corresponding 3-ketone (X) was achieved by oxidation with *N*-bromoacetamide in aqueous *tert.*-butanol. Alternatively, mixture *A* was oxidised with *N*-bromoacetamide in aqueous pyridine, and the product acetylated and chromatographed to give the foregoing monoketone and the diketone (VII; R = β-OAc, R′ = :O).

Dibromination of 12β : 21-diacetoxy-17α-hydroxy*allo*pregnane-3 : 20-dione (X) followed the hoped-for pattern, no evidence for halogenation in the cortical side chain being obtained (cf. Part II, *loc. cit.*; see also Fleisher and Kendall, *J. Org. Chem.*, 1951, **16**, 572). Polarimetric study of the reaction revealed behaviour typical of 2 : 2-dibromination followed by rearrangement to the 2 : 4-dibromo-derivative of (X). The last compound was not isolated, but was treated directly with sodium iodide in acetone (Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077) and then briefly with zinc in acetic acid, to give 12β : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XI).

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube unless otherwise stated. Aluminium oxide (from B.D.H.; chromatography grade) was used.

3β : 12β-*Diacetoxy*-5α : 22α-*spirostan* (I; R = β-OAc, R′ = Ac).—Hecogenin acetate (50 g.) in methanol (1 l.) was heated with sodium hydroxide (25 g.) and water (40 ml.) under reflux for 1 hr. Sodium borohydride (3·0 g.) in methanol (120 ml. of 90%) containing sodium hydroxide (1 g.) was added dropwise during 2 hr., heating being maintained for a further 2 hr.

The product, isolated with chloroform, was acetylated under reflux with pyridine (20 ml.) and acetic anhydride (150 ml.) for 2 hr., percolated in benzene solution through alumina (50 g.) and crystallised from methylene chloride–methanol. It had m. p. 200—202°, $[\alpha]_D^{23}$ −64°, (*c* 0·552 in acetone). Hirschmann, Snoddy, and Wendler (*J. Amer. Chem. Soc.*, 1952, **74**, 2693) give m. p. 202—206·5°, $[\alpha]_D^{23}$ −65° (in acetone).

3β : 12β-*Diacetoxy*allo*pregn*-16-*en*-20-*one* (II; R = β-OAc), prepared from the foregoing compound by Marker and Rohmann's method (*ibid.*, 1940, **62**, 518; see also Wagner, Moore, and Forker, *ibid.*, 1950, **72**, 1856), formed crystals, m. p. 134—135°, $[\alpha]_D^{22\cdot5}$ +18° (*c*, 0·434), $\lambda_{max.}$ 233, 310 mμ (3·96, 1·91) (in *iso*propanol) (Found: C, 72·0; H, 8·9. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·9%).

Hydrogenation of the foregoing compound (100 mg.) in methanol (35 ml.) over 2% palladium–calcium carbonate (500 mg.), followed by hydrolysis and oxidation with chromium trioxide, furnished *allo*pregnane-3 : 12 : 20-trione, m. p. 206—211°. The m. p. was not depressed on admixture with an authentic specimen prepared as described by Wagner *et al.* (*loc. cit.*).

3β-*Acetoxy*-12β-*hydroxy*allo*pregn*-16-*en*-20-*one* (II; R = β-OH).—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (22·5 g.) in ether (1 l.) was heated with lithium aluminium hydride (4 g.) in ether (300 ml.) under reflux for 2 hr.; excess of hydride was decomposed with moist ethyl acetate. The ethereal solution was removed, washed, dried, and evaporated. The residue in benzene (1100 ml.) was dried by distillation (*ca.* 100 ml. removed) and heated with manganese dioxide (30 g.) under reflux for 3 hr. The cooled, filtered solution was taken to dryness and the residue acetylated with acetic anhydride–pyridine overnight in the cold. Crystallisation from methanol furnished 3β-*acetoxy*-12β-*hydroxy*allo*pregn*-16-*en*-20-*one*, m. p. 222—224°, $[\alpha]_D^{23}$ −30° (*c* 0·42) (Found: C, 73·8; H, 9·5. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

3β-*Acetoxy*-12β-*hydroxy*allo*pregnan*-20-*one* (III; R = β-OH, R′ = β-OAc), prepared by hydrogenation of the foregoing compound (1·0 g.) in methanol (20 ml.) over 2% palladium–calcium carbonate, formed prisms, m. p. 150—151°, $[\alpha]_D^{23}$ −14° (*c*, 0·396) (Found: C, 73·5; H, 9·9. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%), after crystallisation from acetone–hexane. Attempted acetylation in the presence of perchloric acid (Reichstein, *Helv. Chim. Acta*, 1953, **36**, 1305) gave an oil from which crystalline material could not be obtained.

Oxidation of the foregoing compound (500 mg.) in acetic acid (20 ml.) with potassium dichromate (480 mg.) in water (4 ml.) at room temperature for 56 hr. furnished 3β-acetoxy*allo*pregnane-12 : 20-dione, m. p. and mixed m. p. 189—192°.

The hydroxy-acetate (III; R = β-OH, R′ = β-OAc) (900 mg.) in methanol (45 ml.) was heated under reflux under nitrogen with aqueous sodium hydroxide (7 ml. of N) for 1 hr. Titration showed that 1 acetyl group had been removed. The crude dihydroxy-compound was oxidised with chromium trioxide (400 mg.) in acetic acid (11 ml.) for 24 hr. at room temperature to give *allo*pregnane-3 : 12 : 20-trione, m. p. and mixed m. p. 206—209°.

3β : 12β-*Diacetoxy*-16α : 17α-*epoxy*allo*pregnan*-20-*one* (V; R = R′ = Ac).—The diacetate (II; R = β-OAc) (10 g.), dissolved in methanol (750 ml.) and water (100 ml.), was treated at 0° with hydrogen peroxide (100 ml. of 30%) and aqueous sodium carbonate (40 ml. of 5%). After 48 hr. the solution was diluted with water and set aside, and the precipitated solids were collected and purified from aqueous methanol. 3β : 12β-*Diacetoxy*-16α : 17α-*epoxy*allo*pregnan*-20-*one* formed needles, m. p. 169—171°, $[\alpha]_D^{23}$ +61° (*c*, 0·462) (Found: C, 69·2; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

3β : 12β-*Diacetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnan*-20-*one* (VI; R = R′ = Ac).—The foregoing compound (5·28 g.) in acetic acid (30 ml.) was treated with hydrogen bromide in acetic acid (3·2 ml. of 50%) for 30 min. at room temperature, after which the mixture was diluted with water and the precipitated solids were purified from methanol. 3β : 12β-*Diacetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnan*-20-*one* formed needles, m. p. 153—154°, $[\alpha]_D^{20}$ +56° (*c*, 0·4386) (Found: C, 57·9; H, 7·3; Br, 15·9. $C_{25}H_{37}O_6Br$ requires C, 58·4; H, 7·2; Br, 15·6%).

3β : 12β-*Diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OAc).—3β : 12β-Diacetoxy-16β-bromo-17α-hydroxy*allo*pregnan-20-one (5 g.) in aqueous methanol (250 ml. of 90%) was hydrogenated over 2% palladium–calcium carbonate (10 g.) at room temperature and atmospheric pressure. Crystallisation of the product from ether–hexane furnished 3β : 12β-*diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one*, needles, m. p. 125—127° or 143—144°, $[\alpha]_D^{23}$ +7° (*c*, 0·326) (Found: C, 69·1; H, 8·8. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

Dehydration of 3β : 12β-*Diacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one*.—(*a*) The diacetate (VII; R = R′ = β-OAc) (200 mg.) in pyridine (2 ml.) was treated at 0° with thionyl chloride (0·06 ml.) added dropwise during 5 min.; then the mixture was poured into water. Crystallisation of the

product from acetone–hexane gave the 17-*sulphite*, m. p. 164—165° (Found: C, 61·1; H, 7·5; S, 7·5. $C_{25}H_{38}O_6S$ requires C, 60·2; H, 7·7; S, 6·4%).

(*b*) The diacetate (VII; R = R′ = β-OAc) (200 mg.) was heated under reflux with phosphorus oxychloride (0·2 ml.) in pyridine (4 ml.) for 30 min. The product, in benzene, was percolated through alumina (6 g.) and then crystallised from hexane, to give 3β : 12β-diacetoxy-*allo*pregn-16-en-20-one, m. p. 136—137° (Found: C, 72·5; H, 8·7. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%), not depressed on admixture with an authentic specimen (above).

3β : 12β : 17α-*Trihydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OH), prisms, m. p. 241—242° (variable), $[\alpha]_D^{18}$ +23° (*c*, 0·218 in EtOH) (Found: C, 71·9; H, 9·8. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%), after crystallisation from methanol, was prepared by hydrolysis of the diacetate (VII; R = R′ = β-OAc) (510 mg.) in methanol (35 ml.) with aqueous sodium hydroxide (10 ml. of 0·5N) for 12 hr. at room temperature.

3β-*Acetoxy*-16α : 17α-*epoxy*-12β-*hydroxy*allo*pregnan*-20-one (V; R = H, R′ = Ac), plates (from acetone), m. p. 233—236°, $[\alpha]_D^{22}$ +38° (*c*, 0·430) (Found: C, 70·5; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), was prepared by treating 3β-acetoxy-12β-hydroxy*allo*pregn-16-en-20-one (1·9 g.) in methanol (240 ml.) and water (30 ml.) with hydrogen peroxide (24 ml. of 30%) and aqueous sodium carbonate (4 ml. of 5%) at 0° for 16 hr.

3β-*Acetoxy*-16β-*bromo*-12β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VI; R = H, R′ = Ac), shimmering leaflets (from ether–chloroform), m. p. 197—198°, $[\alpha]_D^{22}$ +46° (*c*, 0·440) (Found: C, 58·7; H, 7·1; Br, 17·4. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%), was prepared by treating the foregoing compound (800 mg.) in chloroform (16 ml.) and acetic acid (6 ml.) with hydrogen bromide (1·9 ml. of saturated solution in acetic acid) at −30° to −7° for 12 hr.

3β : 12β : 17α-*Trihydroxy*allo*pregnan*-20-*one* (VII; R = R′ = β-OH).—The foregoing compound (750 mg.) in aqueous methanol (70 ml. of 90%) was hydrogenated over 2% palladium–calcium carbonate. The product was chromatographed in benzene on alumina (20 g.). The 1 : 1 ether–benzene eluates yielded a substance (260 mg.; m. p. 84—110°) which was hydrolysed by heating it with potassium carbonate (150 mg.) in methanol (25 ml.) and water (5 ml.) under nitrogen for 1 hr. Crystallisation of the product from methanol yielded the triol (VII; R = R′ = β-OH), m. p. 233—235° (variable), alone or on admixture with a sample prepared as above. Acetylation gave the diacetate (VII; R = R′ = β-OAc).

allo*Pregnane*-3β : 12β : 17α : 20ξ-*tetrol* (VIII).—3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (2 g.) in methanol (300 ml.) and aqueous sodium hydrogen carbonate (2 g. in 100 ml.) was treated with sodium borohydride (1 g.). After 16 hr. at room temperature the product was isolated with chloroform and crystallised from aqueous methanol, yielding allo*pregnane*-3β : 12β : 17α : 20ξ-*tetrol*, m. p. 247—249° (Found: C, 71·1; H, 10·4. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·3%), similarly obtained from the triol (VII; R = R′ = β-OH).

3β : 12β-*Dihydroxyandrostan*-17-*one* (IV), m. p. 179—180° (from acetone–hexane), $[\alpha]_D^{23}$ +62° (*c* 0·3) (Found: C, 74·1; H, 10·2. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%), was prepared by oxidising the foregoing compound (200 mg.) with sodium bismuthate (4 g.) in aqueous acetic acid (40 ml. of 50%) for 12 hr. with vigorous stirring at room temperature.

12β-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VII; R = β OAc, R′ = β OH).—3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (3·2 g.) in methanol (160 ml.) was heated under reflux for 3 hr. with methanolic hydrochloric acid (2·08 ml. of a solution prepared from 0·6 ml. of concentrated hydrochloric acid made up to 5 ml. with methanol). The product was isolated with ether and crystallised from acetone–hexane, to give 12β-*acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one*, needles, m. p. 147° or 163—164°, $[\alpha]_D^{24}$ −6° (*c*, 0·362) (Found: C, 70·5; H, 9·2. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·3%).

12β-*Acetoxy*-16α : 17α-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one* (V; R = Ac, R′ = H).—3β : 12β-Diacetoxy-16α : 17α-epoxy*allo*pregnan-20-one (1 g.) dissolved in methanol (30 ml.) was treated with potassium carbonate (175 mg.) in water (5 ml.) for 15 hr. at room temperature. After precipitation with water the solids were collected and crystallised from aqueous methanol. 12β-*Acetoxy*-16α : 17α-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one* formed plates, m. p. 203—204°, $[\alpha]_D^{23}$ +64° (*c*, 0·530) (Found: C, 70·7; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

12β-*Acetoxy*-16β-*bromo*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VI; R = Ac, R′ = H), needles (from ether–hexane), m. p. 180—182° (decomp.), $[\alpha]_D^{23}$ +62° (*c*, 0·440) (Found: C, 58·9; H, 7·6; Br, 16·6. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%), was prepared by treating the foregoing compound (500 mg.) in chloroform (25 ml.) with hydrogen bromide (0·5 ml. of 50% in acetic acid) at room temperature for 16 hr.

12β-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (VII; R = β-OAc, R′ = β-OH), m. p. 162°, not depressed on admixture with a sample prepared as above, was obtained when the

foregoing compound (570 mg.) in aqueous methanol (30 ml. of 90%) was hydrogenated over 2% palladium–calcium carbonate.

12β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* (VII; R = β-OAc, R′ = :O).—The foregoing compound (110 mg.) in *tert.*-butanol (5 ml.), water (0·2 ml.), and pyridine (0·2 ml.) was treated with *N*-bromoacetamide (110 mg.) for 16 hr. at room temperature. After dilution with water the product was extracted with ether, debrominated by treatment for 10 min. with zinc dust in acetic acid on the steam-bath, and crystallised from acetone–hexane. 12β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* was obtained having m. p. 140·5—141°, $[\alpha]_D^{22}$ +35° (*c*, 0·3352) (Found: C, 70·8; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

12β : 17α-*Dihydroxy*allo*pregnane*-3 : 20-*dione* (VII; R = β-OH, R′ = :O), prepared by oxidising 3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (200 mg.) in pyridine (6 ml.) and water (0·4 ml.) with *N*-bromoacetamide (300 mg., 3 mols.) for 24 hr. at room temperature, followed by brief debromination with zinc and acetic acid at 100°, formed needles, m. p. 220—221°, $[\alpha]_D^{23}$ −8° (*c*, 0·438) (Found: C, 72·0; H, 9·2. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), from aqueous methanol. Acetylation gave the 12-acetate, m. p. 140—141° (Found: C, 70·5; H, 8·9. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%), not depressed on admixture with the product described above.

12β : 21-*Diacetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (IX; R = Ac, R′ = H, R″ = OAc).—A stirred solution of 12β-acetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (2·6 g.) in chloroform (75 ml.) at 40° was treated dropwise with bromine (18 ml. of 0·375M-solution in chloroform). When decolorisation was complete the solution was washed, dried, and evaporated and the residue treated with ether–hexane, to give the crude 21-bromo-derivative (800 mg.; m. p. 121—125°).

The last compound in acetone (30 ml.) was heated with sodium iodide (480 mg.) under reflux for 25 min., the cooled solution was filtered, and potassium hydrogen carbonate (4 g.) and acetic acid (2·4 ml.) were added. After 18 hr. under reflux the mixture was poured into water, and the product isolated with ether and crystallised from acetone–hexane. 12β : 21-*Diacetoxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* formed crystals, m. p. 189—190°, $[\alpha]_D^{24}$ +37° (*c* 0·618) (Found: C, 66·7; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·7; H, 8·5%).

21-*Bromo*-3β : 12β : 17α-*trihydroxy*allo*pregnan*-20-*one* (IX; R = R′ = H, R″ = Br).—3β : 12β : 17α-Trihydroxy*allo*pregnan-20-one (280 mg.) in acetic acid–chloroform (30 ml. of 1 : 1) was stirred at 40° whilst a solution of bromine in chloroform (2·94 ml. of 0·272M) was added dropwise. After decolorisation, the solution was diluted with chloroform and washed with water, dilute sodium carbonate solution, and water, after which it was dried and evaporated under reduced pressure. A portion was triturated with aqueous methanol, to give 21-bromo-3β : 12β : 17α-*trihydroxy*allo*pregnan*-20-*one*, m. p. 205—210° (decomp.), $[\alpha]_D^{26}$ +33° (*c*, 0·418 in EtOH) (Found: C, 61·5; H, 8·2; Br, 15·0. $C_{21}H_{33}O_4Br$ requires C, 58·7; H, 7·7; Br, 18·7%). Recrystallisation led to further loss of bromine.

3β : 12β : 21-*Triacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* (IX; R = R′ = Ac, R″ = OAc).—(*a*) 3β : 12β-Diacetoxy-17α-hydroxy*allo*pregnan-20-one (500 mg.) in chloroform (20 ml.) was brominated at 40° with bromine (4·7 ml. of 0·272M-solution in chloroform). After 40 min. the product was isolated, crystallised from ether–hexane (yield 370 mg.; m. p. 144—145°) and heated in acetone (70 ml.) with sodium iodide (220 mg.) for 30 min. After filtration, potassium hydrogen carbonate (1·85 g.) and acetic acid (1·1 ml.) were added, the mixture was heated under reflux for 20 hr., and the product isolated with ether. After dehalogenation by brief treatment with zinc and acetic acid at 100° and crystallisation from acetone–hexane, 3β : 12β : 21-*triacetoxy*-17α-*hydroxy*allo*pregnan*-20-*one* was obtained as needles, m. p. 199—200°, $[\alpha]_D^{20}$ +26° (*c*, 0·397) (Found: C, 66·1; H, 8·2. $C_{27}H_{40}O_8$ requires C, 65·9; H, 8·1).

(*b*) Crude 21-bromo-3β : 12β : 17α-trihydroxy*allo*pregnan-20-one was converted into the 21-acetoxy-derivative as in (*a*). Acetylation of the product was followed by chromatography in benzene on alumina (10 g.). Elution with benzene–ether furnished 3β : 12β-diacetoxy-17α-hydroxy*allo*pregnan-20-one, m. p. 123—125° alone or on admixture with an authentic specimen (see above). Elution with ether–acetone gave 3β : 12β : 21-triacetoxy-17α-hydroxy*allo*pregnan-20-one, m. p. 197—198° (Found: C, 65·9; H, 8·1%), not depressed on admixture with a sample prepared as above.

(*c*) The same product was obtained by acetylation of 12β : 21-diacetoxy-3β : 17α-dihydroxy-*allo*pregnan-20-one.

12β : 21-*Diacetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione* (X).—(*a*) 12β : 21-Diacetoxy-3β : 17α-dihydroxy*allo*pregnan-20-one (700 mg.) in *tert.*-butanol (30 ml.), water (1 ml.), and pyridine (1 ml.) was treated with *N*-bromoacetamide (800 mg.) for 20 hr. at room temperature. After

debromination (zinc dust in acetic acid for 10 min. at 100°), the product was crystallised from acetone–hexane, to give 12β : 21-*diacetoxy*-17α-*hydroxy*allo*pregnane*-3 : 20-*dione*, m. p. 195—196°, $[\alpha]_D^{24}$ +60° (*c*, 0·432) (Found : C, 66·7; H, 8·0. $C_{25}H_{36}O_7$ requires C, 67·0; H, 8·0%).

(*b*) Crude 21-bromo-3β : 12β : 17α-trihydroxy*allo*pregnan-20-one (700 mg.) was acetoxylated as before. The product in pyridine (24 ml.) and water (1·6 ml.) was oxidised with *N*-bromoacetamide (1·2 g.), briefly debrominated, treated with acetic anhydride (5 ml.) and pyridine (5 ml.) for 1 hr. at 100°, and chromatographed in benzene solution on alumina (20 g.). Elution with benzene–ether (1 : 4) yielded the diacetate (VII; R = R′ = β-OAc). Elution with ether–acetone gave the triacetate (X), m. p. 191—192° (Found : C, 67·7; H, 8·1%).

12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XI).—The foregoing compound (1·28 g.) in acetic acid (130 ml.) was treated dropwise with bromine (27·5 ml. of 0·208M-solution in acetic acid) during 20 min. Hydrogen bromide (2 ml. of 50% w/v solution in acetic acid) was added and after 20 hr. the 2 : 4-dibromide was isolated by means of ether and treated under nitrogen in boiling acetone (80 ml.) with sodium iodide (8 g.) for 22 hr. The mixture was poured into sodium hydrogen sulphite solution and the product was isolated with ether, debrominated (5 g. of zinc dust in 20 ml. of acetic acid for 15 min. at 40°) and crystallised from acetone–hexane, then from aqueous methanol. 12β : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* formed needles, m. p. 153—154°, $[\alpha]_D^{24}$ +103° (*c*, 0·388), $\lambda_{max.}$ 239 mμ (4·19) (in *iso*propanol) (Found : C, 66·7; H, 7·8. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%).

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The Constitution and Stereochemistry of Euphol.

By D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight.

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The triterpenoids euphol and lanosterol are similar in many respects. This is illustrated by parallel reactions carried out on rings B and C of the tetracyclic nucleus and by degradations which demonstrate the presence of an *iso*octenyl side chain in both compounds.

Lanostene and euphene are shown to have the same number of methyl groups. In the light of earlier work this demonstrates that ring D of euphol cannot be six-membered.

Dehydrogenation of euphadiene affords 1 : 7 : 8-trimethylphenanthrene; the same degradation applied to *iso*euphadiene gives 1 : 2 : 5-trimethylnaphthalene. This evidence provides strong support for the view that migration of a methyl group is involved in the conversion of euphenol into *iso*euphenol.

A tricyclic diketone from euphenol is shown to have two methylene groupings adjacent to the ketone groups. This observation excludes an earlier formula for euphol.

The constitution and stereochemistry shown in (I; R = OH) are advanced to explain these and earlier observations on the chemistry of euphol.

The triterpenoid alcohol euphol, a major constituent of dried euphorbia latex, was first isolated in a state of purity by Newbold and Spring (*J.*, 1944, 249). In the last decade this compound has been the subject of detailed structural investigation. The present paper summarises new experimental work which, when combined with previous studies cited in detail below, throws considerable light on the constitutional and stereochemical problems involved. Our views on these subjects can be conveniently summarised in the expression (I; R = OH) for euphol. A preliminary communication to this effect has already appeared (Barton, McGhie, Pradhan, and Knight, *Chem. and Ind.*, 1954, 1325).

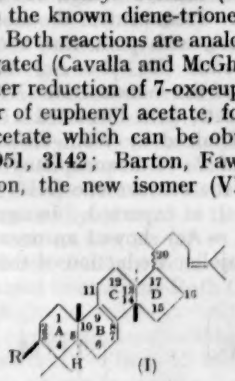
We commence our exposition by reporting work (for preliminary communications see

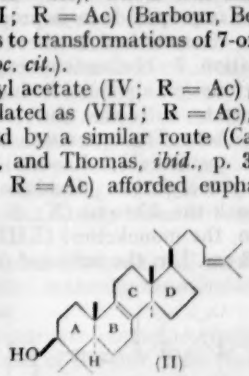
Knight and McGhie, *Chem. and Ind.*, **1953**, 920; **1954**, 24) which, in agreement with that by others (Christen, Dünnenberger, Roth, Heusser, and Jeger, *Helv. Chim. Acta*, **1952**, **35**, 1756, and earlier papers; Barbour, Bennett, and Warren, *J.*, **1951**, 2540, and earlier papers; Vilkas, *Ann. Chim.*, **1951**, **6**, 325, and earlier papers; Dawson, Halsall, and Swayne, *J.*, **1953**, 590), supports a close structural relation between rings A, B, and C of euphol and its side chain and the comparable features of lanosterol (II).

Chromic acid oxidation of euphenyl acetate (III; R = Ac) under mild conditions gives 7-oxoeuphenyl acetate (IV; R = Ac) in poor yield (McDonald, Warren, and Williams, *J.*, **1949**, S 155; see Christen *et al.*, *loc. cit.*). This oxidation can be carried out more efficiently with ozone or, alternatively, by treating euphadienyl acetate (V; R = Ac) with performic or perphthalic acid. With the former reagent the unsaturated ketone was formed directly; with the latter a compound, $C_{32}H_{52}O_3$, was isolated which is either an epoxide or the $\beta\gamma$-unsaturated ketone, 7-oxoeuph-9(11)-enyl acetate, for under acid conditions it was smoothly rearranged to the desired (IV; R = Ac). Closely comparable reactions have been reported in the lanosterol series (Birchenough and McGhie, *J.*, **1950**, 1249; Cavalla and McGhie, *J.*, **1951**, **744**; and references there cited).

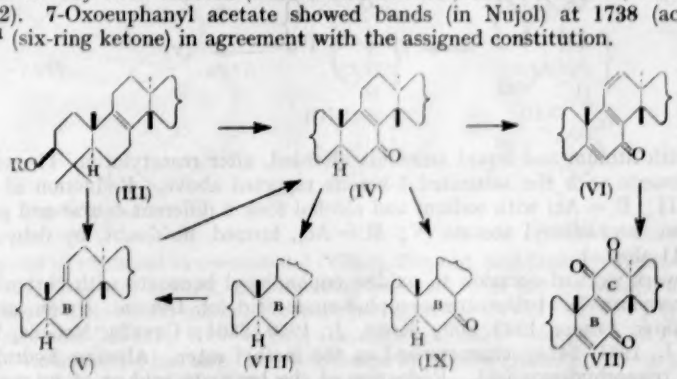
Oxidation of 7-oxoeuphenyl acetate (IV; R = Ac) with selenium dioxide afforded 7-oxoeupha-5 : 8 : 11-trienyl acetate (VI; R = Ac), which was smoothly oxidised by chromic acid to the known diene-trione (VII; R = Ac) (Barbour, Bennett, and Warren, *J.*, **1951**, 2540). Both reactions are analogous to transformations of 7-oxolanostenyl acetate already investigated (Cavalla and McGhie, *loc. cit.*).

Wolff–Kishner reduction of 7-oxoeuphenyl acetate (IV; R = Ac) gave, after reacetylation, an isomer of euphenyl acetate, formulated as (VIII; R = Ac), and comparable to lanost-7-enyl acetate which can be obtained by a similar route (Cavalla, McGhie, and Pradhan, *J.*, **1951**, **3142**; Barton, Fawcett, and Thomas, *ibid.*, p. 3147). On selenium dioxide oxidation, the new isomer (VIII; R = Ac) afforded euphadienyl acetate (V; R = Ac).


(I)


(II)

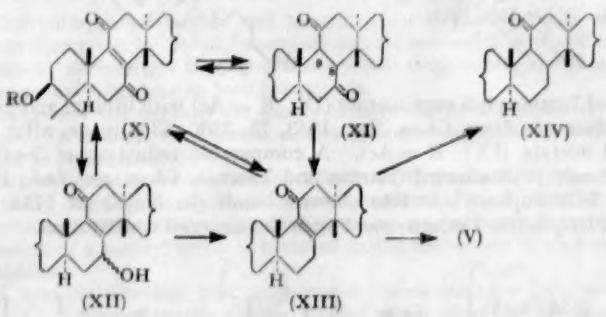
Reduction of 7-oxoeuph-8-enyl acetate (IV; R = Ac) with lithium and liquid ammonia (Wilds and Nelson, *J. Amer. Chem. Soc.*, **1953**, **75**, 5360, 5366) gave, after reacetylation, 7-oxoeuphanyl acetate (IX; R = Ac). A comparable reduction of 7-oxolanost-8-enyl acetate has already been effected (Barton and Thomas, *Chem. and Ind.*, **1953**, **172**; *J.*, **1953**, 1842). 7-Oxoeuphanyl acetate showed bands (in Nujol) at 1738 (acetate) and 1716 cm.$^{-1}$ (six-ring ketone) in agreement with the assigned constitution.


(III) (IV) (VI) (V) (VIII) (IX) (VII)

Reduction of 7 : 11-dioxoeuphenyl benzoate (X; R = Bz) (Vilkas, Dupont, and Dulou, *Bull. Soc. chim. France*, **1949**, **813**) with zinc dust and acetic acid furnished the

saturated diketone (XI; R = Bz). The reduction is comparable to that observed in the lanosterol series (Dorée, McGhie, and Kurzer, *J.*, 1949, 988; cf. Christen *et al.*, *loc. cit.*). However, whilst 7 : 11-dioxolanost-8-enyl acetate is reduced to a 1 : 4-dione with *trans*-fusion of rings B and C, the diones in the euphol series appear (cf. Barnes and Barton, *J.*, 1952, 1419) to have the two hydrogen atoms at positions 8 and 9 *cis* to each other (Knight and McGhie, *loc. cit.*). Thus 7 : 11-dioxoeuphanyl acetate (XI; R = Ac) (Christen *et al.*, *loc. cit.*) was easily oxidised back to the parent ene-dione (X; R = Ac) by selenium dioxide. Also alkaline hydrolysis of 7 : 11-dioxoeuphanyl benzoate afforded 7 : 11-dioxoeuphenol (X; R = H), and not the saturated diketone (XI; R = H).

7 : 11-Dioxolanostanyl acetate can easily be obtained from 7 : 11-dioxolanost-8-enyl acetate by catalytic hydrogenation (Dorée, McGhie, and Kurzer, *loc. cit.*) as well as by zinc dust reduction (see above). In contrast, catalytic hydrogenation of 7 : 11-dioxoeuph-8-enyl acetate gives a dihydro-derivative which is still an unsaturated ketone (Haines and Warren, *J.*, 1950, 1562; Barbour and Warren, *Chem. and Ind.*, 1952, 295). Of the various possible formulæ for this compound (Dawson, Halsall, and Swayne, *loc. cit.*), we have established that (XII; R = Ac) is correct. Reduction of 7 : 11-dioxoeuph-8-enyl acetate with sodium borohydride gave a compound identical with that obtained by catalytic hydrogenation. The reduction was also effected, although less conveniently, by the use of aluminium *iso*propoxide in *iso*propanol. Treatment of the monoacetate (XII; R = Ac), which was characterised as the diacetate, with potassium *tert.*-butoxide gave back, after reacetylation, 7 : 11-dioxoeuphenyl acetate (X; R = Ac), no doubt *via* the saturated 7 : 11-diketone (cf. above). Reduction of the monoacetate (XII; R = Ac), or of the derived diacetate, with zinc dust and acetic acid furnished 11-oxoeuph-8-enyl acetate (XIII; R = Ac). The latter was also obtained by Wolff–Kishner reduction of 7 : 11-dioxoeuphenyl acetate (X; R = Ac) or of 7 : 11-dioxoeuphanyl benzoate (XI; R = Bz), followed by acetylation. Oxidation of the monoketone (XIII; R = Ac) with chromic acid gave back the diketone (X; R = Ac), as expected. In agreement with its assigned constitution, the monoketone (XIII; R = Ac) showed an unsaturated six-ring ketone band at 1673 cm.$^{-1}$ in the infra-red (in Nujol). Reduction of this ketone (XIII;



R = Ac) with lithium and liquid ammonia afforded, after reacetylation, 11-oxoeuphanyl acetate, isomeric with the saturated 7-ketone reported above. Reduction of the same ketone (XIII; R = Ac) with sodium and alcohol took a different course and gave, after reacetylation, euphadienyl acetate (V; R = Ac), formed, no doubt, by dehydration of the allylic 11-alcohol.

In our work we had occasion to oxidise euphadienyl benzoate with chromic acid, to give 3β-benzoyloxy-7 : 11-dioxotrisnoreuph-8-enoic acid (cf. Dupont, Dulou, and Vilkas, *Bull. Soc. chim. France*, 1949, 809; Krüsi, *J.*, 1950, 2864; Cavalla, McGhie, Pickering, and Rees, *J.*, 1951, 2474), characterised as the methyl ester. Alkaline hydrolysis gave the known trisnorhydroxy-acid. Reduction of the benzoate acid or of its methyl ester with zinc dust and acetic acid gave the expected dihydro-derivatives. That from the methyl ester was re-oxidised by selenium dioxide to its precursor. Similarly, the methyl

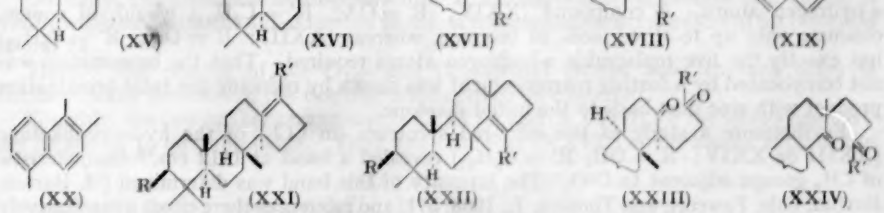
ester of the trisnorhydroxy-acid and its derived acetate were smoothly reduced by zinc dust to the corresponding saturated diketones. Treatment of 3β-hydroxy-7 : 11-dioxotrisnoreuph-8-enoic acid with sodium borohydride afforded the expected 7ξ-hydroxy-compound, reduced by zinc dust to 3β-hydroxy-11-oxotrisnoreuph-8-enoic acid. The latter was also prepared by Wolff–Kishner reduction of the above-mentioned diketo-acid. Selenium dioxide oxidation of the diketo-acid gave the hitherto unknown 3β-hydroxy-7 : 11 : 12-trioxotrisnoreupha-5 : 8-dienoic acid.

The presence of an *iso*octenyl side chain in euphol, identical with that of lanosterol, was established by degradational experiments by Christen, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1951, **34**, 1675). Direct confirmation of this conclusion has been secured (see Knight and McGhie, *loc. cit.*) by vigorous chromic acid oxidation of euphenyl acetate which gave, in small yield, 6-methylheptan-2-one and acetone. Corresponding degradations have been reported on cholesterol (Windaus, *Ber.*, 1913, **46**, 1246; Dirscherl and Nahm, *Annalen*, 1943, **555**, 57) and on lanostenyl acetate (Barton, McGhie, *et al.*, *Chem. and Ind.*, 1951, 1067).

The chemistry of euphol has now reached a position where the nature of rings A, B, and C and of the side chain can be taken as established. The size of ring D as five-membered is implied by experiments of the Zürich group cited by Ruzicka (with Eschenmoser and Heusser, *Experientia*, 1953, **9**, 357). We have shown that ring D is almost certainly *cyclo*pentanic by a quantitative comparison of the infra-red maxima of lanostene (XV; $R' = C_8H_{17}$) and euphene (XVI; $R' = C_8H_{17}$) in the 1380-cm.$^{-1}$ region of the spectrum (in CCl_4). This region is characteristic for the C–H bending of methyl groups (for example, see Barton, Page, and Warnhoff, *J.*, 1954, 2715, and references there cited). Measured at the same concentration, the curves for lanostene and euphene are identical near 1380 cm.$^{-1}$. This shows that both compounds must have the same number (eight) of methyl groups. With allowances for the fourteen carbon atoms in rings A, B, and C, and the five carbon atoms (other than methyl groups) in the side chain, only three carbon atoms are unplaced with which to construct ring D.

Further evidence that lanostenol and euphenol contain the same number of methyl groups was obtained from Kuhn–Roth *C*-methyl determinations (lanostenol 12·9, euphenol 13·3% of *C*-methyl).

The remaining uncertainties about the constitution of euphol are the position of two methyl groups (now placed at positions 13 and 14) and of the side chain (now placed at position 17). Any satisfactory constitutional proposals must also explain the acid-catalysed



rearrangement of euphenol to *iso*euphenol (Vilkas, Dupont, and Dulou; Christen, Dünnenberger, *et al.*; Dawson, Halsall, and Swayne, *locc. cit.*). Of the formulations that have been considered hitherto for euphol the most pertinent are (XVII; $R' = C_8H_{15}$) (Christen *et al.*, *loc. cit.*) and (XVIII; $R' = C_8H_{15}$) (Ruzicka, *loc. cit.*). The possibility that euphol could be 14-*iso*lanosterol has also been mentioned in passing (Ruzicka, *loc. cit.*).

We consider first the nature of the *iso*euphenol rearrangement. This could involve either the movement of the ethylenic linkage (cf. the isomerisation of Δ^8- to Δ^{14}-stenols) or migration of the methyl groups induced by formation of a carbonium ion. Now

dehydrogenation of lanostene affords 1 : 2 : 8-trimethylphenanthrene (XIX) (Barton, Fawcett, and Thomas, *J.*, 1951, 3147; Voser, Mijovic, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1585), the two adjacent methyl groups corresponding to those attached originally at $C_{(13)}$ and $C_{(14)}$. Comparable dehydrogenation of euphadiene (I; R = H) (cf. unpublished work mentioned by Christen *et al.*, *loc. cit.*; McDonald, Warren, and Williams, *J.*, 1949, S 155) also afforded 1 : 2 : 8-trimethylphenanthrene as sole isolatable product. In contrast, dehydrogenation of *iso*euphadiene, prepared from euphadiene (I; R = H) by acid-catalysed rearrangement in the usual way, gave 1 : 2 : 5-trimethylnaphthalene (XX). In spite of careful fractionation no 1 : 2 : 8-trimethylphenanthrene could be detected. That the side-chain *iso*propylidene group of euphadiene was not complicating the course of the rearrangement was shown by ozonolysis of *iso*euphadiene which gave the expected acetone.

The simplest interpretation of these critical experiments is that methyl groups are attached at positions 13 and 14 in euphadiene and that conversion into *iso*euphadiene involves migration of a methyl group from position 14 to position 8. There are then two possible expressions for *iso*euphadiene, namely (XXI; R = H, R′ = C_8H_{15}), which results from the migration of two methyl groups, and (XXII; R = H, R′ = C_8H_{15}) whose formation involves migration of only one methyl group.

In support of the attachment of two methyl groups at positions 13 and 14, we have shown that 7 : 11 : 12-trioxoeupha-5 : 8-dienyl acetate cannot be brominated even under vigorous conditions. This is in agreement with the absence of hydrogen from position 14.

Christen *et al.* (*loc. cit.*) have already shown that ozonolysis of *iso*euphenyl acetate affords a crystalline diketone. On the basis of (XXI or XXII; R = OAc, R′ = C_8H_{17}) for *iso*euphenyl acetate the diketone must be (XXIII or XXIV respectively; R = OAc, R′ = C_8H_{17}). We have accumulated decisive evidence in favour of (XXIII; R = OAc, R′ = C_8H_{17}) for the diketone and thus of (XXI; R = OAc, R′ = C_8H_{17}) for *iso*euphenyl acetate. The diketone forms a dioxime (Christen *et al.*, *loc. cit.*). It would be unexpected if a compound such as (XXIV; R = OAc, R′ = C_8H_{17}) furnished more than a monoxime. The formation of a dioxime from (XXIII; R = OAc, R′ = C_8H_{17}) would, however, be acceptable (cf., for discussion, Barton, *J.*, 1953, 1027). The diketone in question consumes five mols. on titration with bromine (see Table), thus indicating at least five replaceable

Compound	No. of α-hydrogen	Uptake of Br (mols.) *				
Time (days):		1	2	3	4	5
Cholestan-3-one	4	2·72	3·56	3·74	3·89	4·01
Diketone (XXIII; R = OAc, R′ = C_8H_{17})	5	4·52	4·75	4·94	5·00	5·05
Lanostane-3 : 7-dione †	6	2·78	3·09	3·28	3·37	3·42

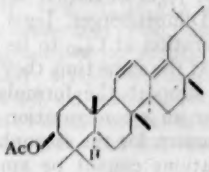
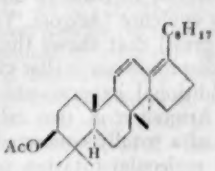
* Brominations were carried out at 37° as detailed on p. 886.
† Dorée, McGhie, and Kurzer, *J.*, 1948, 988.

α-hydrogen atoms. A compound (XXIV; R = OAc, R′ = C_8H_{17}) would, of course, consume only up to three mols. of bromine, whereas (XXIII; R = OAc, R′ = C_8H_{17}) has exactly the five replaceable α-hydrogen atoms required. That the bromination was not complicated by a further rearrangement was shown by reducing the total bromination product with zinc dust back to the initial diketone.

Furthermore a study of the infra-red spectrum (in CCl_4) of the hydroxy-diketone (XXIII or XXIV; R = OH, R′ = C_8H_{17}) revealed a band at 1412 cm.$^{-1}$ characteristic of CH_2 groups adjacent to C=O. The intensity of this band was determined (cf. Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571, and references there cited) quantitatively relative to the corresponding band (at 1420 cm.$^{-1}$) due to two CH_2·CO groups in α-amyrane-3 : 12-dione (kindly supplied by Mr. K. H. Overton). In this way it was shown that there must be two ·CH_2·CO groups in the hydroxy-ketone, which must be formulated, therefore, as (XXIII; R = OH, R′ = C_8H_{17}).

The new constitution (XXI; R = OAc, R′ = C_8H_{17}) for *iso*euphenyl acetate must also, of course, permit the formulation of *iso*euphadienyl acetate (Vilkas, *Bull. Soc. chim. France*, 1950, 582; *Ann. Chim.*, 1951, **6**, 325), the conjugated diene obtained by acid-catalysed dehydration of *iso*euphenyl acetate oxide. The ultra-violet absorption spectrum

of *iso*euphadienyl acetate with its triple peak is very similar to that of olea-11 : 13(18)-dienyl acetate (XXV) (Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767; Barton and Brooks, *J.*, 1951, 257). A probable structure for *iso*euphadienyl acetate is, therefore, (XXVI). In agreement with this formula the infra-red spectra of olea-11 : 13(18)-dienyl

(XXV)   (XXVI)

acetate and of *iso*euphadienyl acetate (in CS_2) were almost identical in the 700—800-cm.$^{-1}$ region. Olea-11 : 13(18)-dienyl acetate showed bands at 729, 759, and 778 cm.$^{-1}$ and *iso*euphadienyl acetate showed bands at 731, 755, and 772 cm.$^{-1}$, both spectra indicating the grouping *cis*-CH:CH· in a six-membered ring (see Henbest, Meakins, and Wood, *J.*, 1954, 800). Evidence against the formulation (XXVI) for *iso*euphadienyl acetate was, apparently, offered by the findings of Vilkas (*loc. cit.*) that catalytic hydrogenation gave "γ-euphenyl acetate." Olea-11 : 13(18)-dienyl acetate is, of course, readily hydrogenated to olean-13(18)-enyl acetate. A repetition of Vilkas's experiment (*loc. cit.*) (cf. Christen *et al.*, *loc. cit.*) gave back *iso*euphenyl acetate and not "γ-euphenyl acetate." It will be recalled that olea-11 : 13(18)-dienyl acetate is prepared by the selenium dioxide oxidation of β-amyrin acetate (olean-12-enyl acetate). Similar oxidation of *iso*euphenyl acetate gave *iso*euphadienyl acetate. The formula (XXVI) appears from all this evidence to be well supported.

The stereochemistry assigned to the methyl groups at positions 13 and 14 in (I; R = OH) for euphol is based on the following considerations. First, this stereochemistry forces the molecule to assume in rings B and C the unfavourable conformation of two half-boats. We believe that this steric strain provides a *conformational driving force* for methyl-group migration, to give the *iso*euphenol stereochemistry, where all three six-membered rings can adopt the favourable chair conformations. The methyl groups in lanostenol do not, of course, migrate when a carbonium ion is formed at position 8, as in the equilibration of lanost-8- and -7-enyl acetate. There is however no reason why the methyl group at position 14 should move to position 8 since the change would be from a favourable all-chair (or half-chair if one considers the *cyclo*hexene rings) conformation to a relatively unfavourable conformation. We are of the opinion that more attention should be paid to conformational effects of this type in considering the likely incidence of carbonium-ion rearrangements in alicyclic systems.

Secondly, the abnormal hydrogenation of 7 : 11-dioxoeuphenyl acetate (see above) is readily explained with the aid of models based on the stereochemistry indicated for positions 13 and 14.

Thirdly, the placing of the $C_{(13)}$- and $C_{(14)}$-methyl groups *trans* to each other is mechanistically desirable if the two migrations are to be concerted.

Fourthly, the two further arrangements (XXVII) and (XXVIII) for the stereochemistry can be shown to be improbable. Thus, the structure (XXVII) could hardly explain the

(XXVII) (XXVIII)

failure (Christen *et al.*, *loc. cit.*) of euphenyl acetate to react with osmium tetroxide under conditions where Δ^8-stenols react readily (Barton and Cox, *J.*, 1949, 214; Djerassi, Yashin, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 422) and the nuclear double bond of lanosterol is untouched (Wieland and Benend, *Z. physiol. Chem.*, 1942, **274**, 215). The stereochemistry of (XXVIII) would not be compatible with the marked steric hindrance shown by the 11-oxo-grouping in the appropriate euphol derivatives (see above).

The configurations assigned to ring A have already been discussed (cf. Christen *et al.*, *loc. cit.*) adequately in our preliminary communication (Barton, McGhie, Pradhan, and Knight, *loc. cit.*) and need not be repeated here. Our tentative assignments of configuration at $C_{(17)}$ and $C_{(20)}$ made in the same article were based on molecular-rotation considerations. Professor L. Ruzicka and Dr. O. Jeger of Zürich have been kind enough to inform us of new evidence (Arigoni, Viterbo, Dünnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, in the press) that shows the configuration at $C_{(20)}$ to be the same as that in lanosterol and thus disproves our earlier views. At the same time they have communicated to us details of additional experiments which support the formula (I; R = OH) for euphol. Although Arigoni *et al.* (*loc. cit.*) favour an α-configuration at $C_{(17)}$ for the side chain, on the basis of a totally concerted mechanism for the *iso*euphenol rearrangement, we believe that, if molecular-rotation considerations cannot be applied, then the non-committal symbol of (I; R = OH) is all that is justified at the present time. Dr. T. G. Halsall has also kindly informed us of unpublished experiments, carried out at Manchester, on the chromic acid oxidation of *iso*euphenyl acetate. The results obtained are incompatible with the earlier formulæ for this acetate, but can be interpreted in terms of (XXI; R = OAc, R′ = C_8H_{17}) (see above).

Experimental

Rotations are for $CHCl_3$ solutions unless stated otherwise; ultra-violet absorption spectra were taken in ethanol on the Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Mr. D. Orr of the Chester Beatty Research Institute and by Messrs. Glaxo Laboratories Ltd.

Light petroleum refers to the fraction of b. p. 60—80° unless specified to the contrary.

7-Oxoeuph-8-enyl Acetate.—(*a*) Eupha-7 : 9(11)-dienyl acetate (Vilkas, *Bull. Soc. chim. France*, 1950, 582; Barbour, Bennett, and Warren, *J.*, 1951, 2540) (500 mg.) in chloroform (2·5 ml.) and formic acid (99—100%; 25 ml.) was heated to 60° and to the well-stirred solution hydrogen peroxide (30%; 1 ml.) was added. The stirred mixture was allowed to cool to room temperature (2 hr.). Chromatography over alumina (12 × 1 cm.) and elution with benzene–light petroleum gave 7-oxoeuph-8-enyl acetate (50 mg.), m. p. (from aqueous methanol) 162—164°.

(*b*) Euphenyl acetate (1·0 g.) in ethyl acetate (25 ml.) was ozonised (4% ozone) at −5° for 2 hr. After being washed with ferrous sulphate solution, the ethyl acetate was removed *in vacuo* and the product chromatographed over alumina (12 × 1 cm.). Elution with 7 : 1 benzene–light petroleum gave 7-oxoeuph-8-enyl acetate (170 mg.), m. p. (from aqueous methanol) 169—170°, $[\alpha]_D$ +35° (*c*, 0·90), $\lambda_{max.}$ 255 mμ (log ε 4·05) (Found: C, 79·0; H, 10·8. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%).

(*c*) Eupha-7 : 9(11)-dienyl acetate (500 mg.) was treated with ethereal perphthalic acid (1·5 mols.) at room temperature for 7 days. The product was chromatographed over alumina (7 × 1 cm.), elution being with benzene–light petroleum. Crystallisation from methanol gave a *compound* (240 mg.), m. p. 119—120°, $[\alpha]_D$ −4° (*c*, 0·3) (Found: C, 78·8; H, 10·55. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). This compound (500 mg.) in acetic acid (15 ml.) was treated with concentrated sulphuric acid (2 drops) under reflux for 10 min. Crystallisation of the product from aqueous methanol afforded 7-oxoeuph-8-enyl acetate (300 mg.), m. p. and mixed m. p. 167—169°, $[\alpha]_D$ +33° (*c*, 0·3), $\lambda_{max.}$ 255 mμ (log ε 3·96).

Dehydrogenation of 7-Oxoeuph-8-enyl Acetate with Selenium Dioxide.—7-Oxoeuph-8-enyl acetate (88·5 mg.) in acetic acid (10 ml.) with selenium dioxide (60 mg.) was heated under reflux for 3 hr. Crystallisation of the product from aqueous methanol gave *7-oxoeupha-5 : 8 : 11-trienyl acetate* (50 mg.) as small plates, m. p. 188—189°, $[\alpha]_D$ −12° (*c*, 0·2), $\lambda_{max.}$ 256 and 327 mμ (log ε 3·9 and 3·9) (Found: C, 79·8; H, 10·0 $C_{32}H_{48}O_3$ requires C, 80·0; H, 10·1%)

This trienone (27 mg.) in acetic acid (5 ml.) was treated at room temperature with chromic acid (27 mg.) in acetic acid (5 ml.). The mixture was then kept at 60—65° for 90 min. Crystallisation from methanol gave 7 : 11 : 12-trioxoeupha-5 : 8-dienyl acetate, m. p. 184—185°, $[\alpha]_D$ −18° (*c*, 0·1), $\lambda_{max.}$ 283 mμ (log ε 3·85), undepressed in m. p. on admixture with an authentic specimen (Barbour, Bennett, and Warren, *J.*, 1951, 2540) of m. p. 189—191°, $[\alpha]_D$ −19° (*c*, 0·6), $\lambda_{max.}$ 284 mμ (log ε 3·9).

Euph-7-enyl Acetate.—7-Oxoeuph-8-enyl acetate (see above) (290 mg.), hydrazine hydrate (100%; 0·4 ml.), and diethylene glycol (12 ml.) were heated at 185° for 1 hr., then cooled to

70°. A solution of sodium (300 mg.) in diethylene glycol (5 ml.) was added, the mixture reheated to 210—220°, and water removed by distillation. After 5 hr. at 210—220°, the product was extracted in the usual way and reacetylated by pyridine (2 ml.) and acetic anhydride (5 ml.) on the steam-bath. Chromatography over alumina (6 × 1 cm.) and elution with light petroleum gave euph-7-enyl acetate, m. p. (from methanol–ethanol) 92—94°, $[\alpha]_D$ −60° (*c*, 0·5) (Found: C, 81·3; H, 11·8. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). Oxidation of this compound (50 mg.) in acetic acid (7 ml.) with selenium dioxide (30 mg.) under reflux for 3 hr., followed by chromatography of the product over alumina (5 × 0·5 cm.) and elution with light petroleum, gave eupha-7 : 9(11)-dienyl acetate, m. p. 109—110°, $[\alpha]_D$ −75° (*c*, 0·2), $\lambda_{max.}$ 232, 239, and 248 mμ (log ε 4·2, 4·3, and 4·15 respectively), undepressed in m. p. on admixture with an authentic specimen (Vilkas, *loc. cit.*) of m. p. 112—113°, $[\alpha]_D$ −80° (*c*, 0·5), $\lambda_{max.}$ 232, 239, and 247 mμ (log ε 4·15, 4·24, and 4·0) (Found: C, 81·9; H, 11·2. Calc. for $C_{32}H_{50}O_2$: C, 82·0; H, 11·2%).

7-Oxoeuphanyl Acetate.—Lithium (30 mg.) was dissolved in dry liquid ammonia (40 ml.), and 7-oxoeuph-8-enyl acetate (200 mg.) in ether (4 ml.) was added. After 10 min. the excess of lithium was destroyed by the addition of 1 : 1 *tert.*-butanol–ether (5 ml.). The product was reacetylated with pyridine–acetic anhydride, and the resultant acetate chromatographed over alumina (7 × 0·5 cm.). Elution with benzene gave *7-oxoeuphanyl acetate* (40 mg.), m. p. (from methanol) 116—117°, $[\alpha]_D$ −72° (*c*, 0·4) (Found: C, 79·1; H, 11·0. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%).

7 : 11-*Dioxoeuphanyl Benzoate.*—7 : 11-Dioxoeuphenyl benzoate {m. p. 186—187°, $[\alpha]_D$ +54° (*c*, 1·10), $\lambda_{max.}$ 272 mμ (log ε 4·12)} (Vilkas, Dupont, and Dulou, *Bull. Soc. chim. France*, 1949, 813) (1·0 g.) in hot acetic acid (20 ml.) was treated under reflux with zinc dust (2·0 g.) added portionwise during 15 min. Crystallisation of the product from methanol gave 7 : 11-*dioxoeuphanyl benzoate*, m. p. 176—177°, $[\alpha]_D$ −90° (*c*, 0·4) (Found: C, 78·7; H, 10·0. $C_{37}H_{54}O_4$ requires C, 78·9; H, 9·8%). Similar reduction of 7 : 11-dioxoeuphanol and its acetate afforded 7 : 11-dioxoeuphanol and its acetate respectively (Christen *et al.*, *Helv. Chim. Acta*, 1952, **35**, 1756). 7 : 11-Dioxoeuphanyl benzoate (700 mg.) was hydrolysed with alcoholic potassium hydroxide under reflux for 3 hr. Crystallisation from aqueous methanol gave 7 : 11-dioxoeuph-8-enol, m. p. 118—119°, $[\alpha]_D$ +25° (*c*, 0·3), $\lambda_{max.}$ 272 mμ (log ε 3·9), identical with a specimen, m. p. 119—120°, $[\alpha]_D$ +26° (*c*, 0·3), obtained in the same way from 7 : 11-dioxoeuphenyl acetate.

7 : 11-Dioxoeuphanyl acetate (500 mg.) in acetic acid (20 ml.) was refluxed with selenium dioxide (250 mg.), dissolved in a minimum of water, for 90 min. Chromatography of the product over alumina (10 × 1 cm.), elution with light petroleum, and crystallisation from methanol gave 7 : 11-dioxoeuph-8-enyl acetate, identified by m. p., mixed m. p., rotation, and absorption spectrum.

Wolff–Kishner Reduction of 7 : 11-*Dioxoeuph-8-enyl Acetate.*—The diketone (3·0 g.) in diethylene glycol (150 ml.) and hydrazine hydrate (100%; 3 ml.) was heated for 1 hr. at 185—190°, then cooled to 70°. Sodium (3·0 g.), dissolved in diethylene glycol (30 ml.), was added and the mixture refluxed at 220° for 6 hr. The product was acetylated with pyridine (5 ml.) and acetic anhydride (10 ml.) overnight at room temperature and then chromatographed over alumina (15 × 1 g.). Elution with light petroleum (500 ml.) and with benzene–light petroleum (800 ml.) gave 11-*oxoeuph-8-enyl acetate* (1·5 g.), m. p. (from methanol) 130—131°, $[\alpha]_D$ +28° (*c*, 0·4), $\lambda_{max.}$ 255 mμ (log ε 3·99) (Found: C, 79·6; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Wolff–Kishner reduction of 7 : 11-dioxoeuphanyl benzoate (see above) likewise afforded 11-oxoeuph-8-enyl acetate, identical (m. p., mixed m. p., rotation, and absorption spectrum) with the material described above.

Reduction of 11-oxoeuph-8-enyl acetate (200 mg.) in *iso*propanol (20 ml) with sodium under reflux until saturated and heating the product with pyridine (2 ml.) and acetic anhydride (5 ml.) on the water-bath for 2 hr. gave eupha-7 : 9(11)-dienyl acetate, identified by m. p., mixed m. p., rotation, and absorption spectrum.

11-Oxoeuph-8-enyl acetate (100 mg.) in acetic acid (5 ml.) was treated with chromic acid (100 mg.) in acetic acid (90%; 5 ml.) at 50° for 1 hr. Chromatography over alumina, elution with light petroleum, and crystallisation from methanol furnished 7 : 11-dioxoeuph-8-enyl acetate, identified by m. p., mixed m. p., rotation, and absorption spectrum.

11-*Oxoeuphanyl Acetate.*—To a stirred solution of lithium (10 mg.) in liquid ammonia (25 ml.), 11-oxoeuph-8-enyl acetate (500 mg.) in dry ether (5 ml.) and small pieces of metallic lithium (40 mg.) were added at such a rate that the initial blue colour was just maintained. After completion of the addition the mixture was stirred for a further 10 min. before adding ammonium chloride (4 g.) and allowing the whole to warm to room temperature. Acetylation

of the product with pyridine (3 ml.) and acetic anhydride (10 ml.) for 2 hr. on the water bath, chromatography over alumina (6 × 0·5 cm.), and elution with 4 : 1 light petroleum–benzene gave 11-*oxoeuphanyl acetate*, m. p. (from methanol) 140—141°, $[\alpha]_D$ −51° (*c*, 0·3) (Found: C, 78·6; H, 11·0. $C_{33}H_{54}O_3$ requires C, 78·9; H, 11·2%).

Reduction of 7 : 11-*Dioxoeuph-8-enyl Acetate with Sodium Borohydride*.—The diketone (1·0 g.) in methanol (40 ml.) was treated with sodium borohydride (700 mg.) in methanol (10 ml.) at room temperature for 24 hr. Crystallisation from aqueous methanol afforded 7ξ-*hydroxy*-11-*oxoeuph*-8-*enyl acetate*, m. p. 204—205°, $[\alpha]_D$ −3° (*c*, 0·7), $\lambda_{max.}$ 257 mμ (log ε 3·9) (Found: C, 76·7; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·7; H, 10·5%). Acetylation with pyridine (2 ml.) and acetic anhydride (8 ml.) at room temperature for 14 hr. gave the *diacetate*, m. p. (from methanol) 127—128°, $[\alpha]_D$ ±0° (*c*, 0·2), $\lambda_{max.}$ 257 mμ (log ε 3·9) (Found: C, 75·0; H, 9·8. $C_{34}H_{54}O_5$ requires C, 75·2; H, 10·0%). The hydroxy-acetate was identical [m. p., mixed m. p., rotation, absorption spectrum, and analysis (Found: C, 76·6; H, 10·35%)] with the compound obtained earlier by Barbour and Warren (*Chem. and Ind.*, 1952, 295) by catalytic hydrogenation of 7 : 11-dioxoeuphenyl acetate.

The diacetate (see above) was also obtained as follows. 7 : 11-Dioxoeuph-8-enyl acetate (1·0 g.) in dioxan (10 ml.) with aluminium *iso*propoxide (6·0 g.) in *iso*propanol (25 ml.) was heated under reflux for 1 hr. The *iso*propanol was then slowly distilled off until no more acetone was evolved (2 : 4-dinitrophenylhydrazine). The refluxing was then repeated for 1 hr., being followed by distillation. This was repeated 14 times, dry *iso*propanol being added after each distillation to maintain a constant volume. Acetylation with pyridine and acetic anhydride, chromatography over alumina (12 × 1 cm.), and elution with 1 : 2 benzene–light petroleum gave the diacetate, identified by m. p., mixed m. p., rotation, and absorption spectrum.

7ξ-Hydroxy-11-oxoeuph-8-enyl acetate (500 mg.) in acetic acid–acetic anhydride (1 : 1; 80 ml.) was heated under reflux for 15 min. with zinc dust (3·0 g.). The product crystallised readily from methanol, to give 11-oxoeuph-8-enyl acetate (300 mg.) identified by m. p., mixed m. p., rotation, absorption spectrum, and analysis (Found: C, 79·1; H, 10·7. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%). Similar reduction of the analogous diacetate (see above) also afforded 11-oxoeuph-8-enyl acetate, identified as indicated above.

7ξ-Hydroxy-11-oxoeuph-8-enyl acetate (500 mg.) in *tert.*-butanol (40 ml.) containing potassium (570 mg.) was heated under reflux for 1 hr. The product was acetylated with pyridine (3 ml.) and acetic anhydride (15 ml.) on the steam-bath for 2 hr. Chromatography over alumina, elution with light petroleum, and crystallisation from methanol afforded 7 : 11-dioxoeuph-8-enyl acetate (150 mg.), identified by m. p., mixed m. p., rotation, and absorption spectrum.

Attempted Bromination of 7 : 11 : 12-*Trioxoeupha*-5 : 8-*dienyl Acetate*.—The diene-trione (Barbour, Bennett, and Warren, *J.*, 1951, 2540) (250 mg.) in acetic acid (10 ml.) was treated in the cold with a solution of bromine (1 ml.; 3% v/v) in acetic acid and 48% hydrobromic acid–acetic acid (one drop) and then heated for 1 hr. at 80°. The product was identified as unchanged starting material by m. p., mixed m. p., rotation, and absorption spectrum. The same result was observed after 90 minutes' heating at 100°.

Chromic Acid Oxidation of Euphadienyl Benzoate.—The benzoate (10 g.) in acetic acid (1 l.) at 55° was treated with chromic acid (20 g.) in acetic acid (90%; 150 ml.) added with stirring during 1 hr. The stirring was continued for a further 90 min. The solution was poured into dilute sulphurous acid, and the yellow precipitate was collected, dissolved in ether, and extracted with dilute potassium hydroxide solution. The acid thus extracted was recovered in the usual way and crystallised from aqueous acetone or from methanol, to give 3β-*benzoyloxy*-7 : 11-*dioxotrisnoreuph*-8-*enoic acid*, m. p. 202—203°, $[\alpha]_D$ +44° (*c*, 0·5), $\lambda_{max.}$ 272 mμ (log ε 4·1) (Found: C, 74·5; H, 8·7. $C_{34}H_{44}O_6$ requires C, 74·5; H, 8·4%). The *methyl ester*, prepared with diazomethane, had m. p. 164—165°, $[\alpha]_D$ +44° (*c*, 0·5) (Found: C, 74·9; H, 8·3. $C_{35}H_{46}O_6$ requires C, 74·7; H, 8·3%). Similar oxidation of euphadienyl acetate gave an acid fraction which on methylation afforded the known (Krüsi, *J.*, 1950, 2864; Bennett, Krüsi, and Warren, *J.*, 1951, 2534) acetate methyl ester (Found: C, 71·7; H, 8·8. Calc. for $C_{30}H_{44}O_8$: C, 71·9; H, 8·9%).

Methyl 3β-benzoyloxy-7 : 11-dioxotrisnoreuph-8-enoate (4·0 g.) in acetic acid (100 ml.) was treated under reflux with zinc dust (10 g.) added portionwise during 15 min. After a further 20 minutes' refluxing the product, isolated in the usual way, crystallised from chloroform–methanol to give *methyl* 3β-*benzoyloxy*-7 : 11-*dioxotrisnoreuphanoate*, m. p. 191—192°, $[\alpha]_D$ −98° (*c*, 0·4) (Found: C, 74·8; H, 8·6. $C_{35}H_{46}O_6$ requires C, 74·5; H, 8·5%). Dehydrogenation

of this compound with selenium dioxide as described above for 7 : 11-dioxoeuphanyl acetate gave back methyl 3β-benzoyloxy-7 : 11-dioxotrisnoreuph-8-enoate.

The trisnor-acid benzoate (see above) (7·0 g.) in methanol (25 ml.) was treated with ethanolic potassium hydroxide (7%; 300 ml.) under reflux for 3 hr. Crystallisation from ethyl acetate gave 3β-hydroxy-7 : 11-dioxotrisnoreuph-8-enoic acid (Dupont, Dulou, and Vilkas, *Bull. Soc. chim. France*, 1949, 809) (4·0 g.), m. p. 232—233°, $[\alpha]_D$ −9° (*c*, 0·7 in pyridine), $\lambda_{max.}$ 271 mμ (ε 9500).

Zinc dust reduction of methyl 3β-hydroxy-7 : 11-dioxotrisnoreuph-8-enoate as for the benzoate methyl ester (see above) gave the corresponding saturated *diketone*, m. p. 166—168°, $[\alpha]_D$ −142° (*c*, 0·9) (Found : C, 73·2; H, 9·8. $C_{25}H_{44}O_5$ requires C, 73·0; H, 9·7%). The corresponding *acetate methyl ester*, prepared similarly, had m. p. 216—218°, $[\alpha]_D$ −116° (*c*, 0·4) (Found : C, 71·2; H, 9·1. $C_{30}H_{46}O_6$ requires C, 71·7; H, 9·3%). The corresponding *benzoate acid* had m. p. 195—197°, $[\alpha]_D$ −100° (*c*, 0·2) (Found : C, 73·0; H, 8·6. $C_{34}H_{46}O_6$ requires C, 73·2; H, 8·4%).

3β : 7ξ-*Dihydroxy*-11-*oxotrisnoreuph*-8-*enoic Acid*.—The 7 : 11-dioxo-acid (see above) (500 mg.) in methanol (25 ml.) was treated with sodium borohydride (400 mg.) in methanol (15 ml.) for 24 hr. at room temperature. Crystallisation of the product from aqueous methanol afforded 3β : 7ξ-*dihydroxy*-11-*oxotrisnoreuph*-8-*enoic acid*, m. p. 232—233°, $[\alpha]_D$ −44° (*c*, 0·7 in pyridine), $\lambda_{max.}$ 257 mμ (log ε 3·85) (Found : C, 72·4; H, 9·3. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%). The acid (130 mg.) and zinc dust (500 mg.) in acetic acid (15 ml.) were heated on the steam-bath for 2 hr. Crystallisation of the product from aqueous acetone gave 3β-*hydroxy*-11-*oxotrisnoreuph*-8-*enoic acid*, m. p. 224—226°, $\lambda_{max.}$ 256 mμ (log ε 3·8) (Found : C, 75·6; H, 10·1. $C_{27}H_{44}O_4$ requires C, 75·3; H, 9·85%). This acid was also prepared by Wolff–Kishner reduction as detailed for the analogous 7 : 11-dioxoeuph-8-enyl acetate (see above).

Selenium Dioxide Oxidation of 3β-*Hydroxy*-7 : 11-*dioxotrisnoreuph*-8-*enoic Acid*.—The acid (650 mg.), selenium dioxide (450 mg.), and dioxan (15 ml.) were heated together in a sealed tube at 180° for 4 hr. Crystallisation of the product from aqueous acetone (charcoal) gave 3β-*hydroxy*-7 : 11 : 12-*trioxotrisnoreupha*-5 : 8-*dienoic acid* (250 mg.), m. p. 202—203°, $[\alpha]_D$ −20° (*c*, 0·4), $\lambda_{max.}$ 285 mμ (log ε 3·85) (Found : C, 71·4; H, 7·8. $C_{27}H_{36}O_6$ requires C, 71·0; H 7·95%).

Isolation of 6-*Methylheptan*-2-*one*.—Euphenyl acetate (20 g.) in acetic acid (160 ml.) was heated to boiling in a distillation-flask fitted with condenser, receiver, and dropping funnel. To the boiling mixture chromic acid (60 g.) in acetic acid (80%; 180 ml.) and potassium persulphate (14 g.) in water (100 ml.) were added slowly during 1 hr. The rate of distillation was made equal to the rate of addition. When the addition was complete, aqueous acetic acid (1 : 1; 150 ml.) was added and the equivalent volume distilled off. The combined distillates were neutralised (30% aqueous sodium hydroxide) and the mixture was steam-distilled. The first 100 ml. of distillate were treated with excess of 2 : 4-dinitrophenylhydrazine hydrochloride solution and left at 0° overnight. The precipitate was collected and chromatographed over alumina to give 6-methylheptan-2-one 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 77—78°, $\lambda_{max.}$ 366 mμ (log ε 4·36) (Found : C, 54·4; H, 6·4; N, 18·1. Calc. for $C_{14}H_{20}O_4N_4$: C, 54·5; H, 6·6; N, 18·2%). Subsequent eluates contained acetone 2 : 4-dinitrophenylhydrazone, identified by m. p. and mixed m. p.

Dehydrogenation of Euphadiene.—Euphadiene (Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620; Vilkas, Dupont, and Dulou, *Bull. Soc. chim. France*, 1949, 813; Vilkas, *Ann. Chim.*, 1951, **6**, 325) (19 g.) and selenium powder (38 g.) were heated together at 350° for 48 hr. After cooling, the black residue was ground and extracted under reflux with light petroleum (250 ml.) for 3 hr. After filtration the light petroleum extract was chromatographed over alumina (25 × 2 cm.). Elution with light petroleum (3 × 300 ml.) gave a solid which crystallised from alcohol to give a product, m. p. 105—115°. This was rechromatographed over alumina; elution with light petroleum gave crude 1 : 7 : 8-trimethylphenanthrene (650 mg.) of m. p. 130—136°. Conversion into the picrate gave (from alcohol) 1 : 7 : 8-trimethylphenanthrene picrate (450 mg.), identified by m. p., mixed m. p., and analysis (Found : C, 61·6; H, 4·1; N, 9·7. Calc. for $C_{23}H_{19}O_7N_3$: C, 61·45; H, 4·25; N, 9·35%). The picrate was reconverted into 1 : 7 : 8-trimethylphenanthrene which was identified by m. p. and mixed m. p. (145—146°), ultra-violet absorption spectrum ($\lambda_{max.}$ 215, 226, 254, 262, 283, 294, and 306 mμ; ε 35,100, 18,500, 44,000, 57,000, 12,500, 12,800, and 15,700) and analysis (Found : C, 92·5; H, 7·3. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%).

iso*Euphadiene*.—Euphadiene (2·0 g.) in glacial acetic acid (75 ml.) containing aqueous 2N-sulphuric acid (2 ml.) was refluxed for 2 hr. The product, in light petroleum, was filtered

over alumina (50 g.). Elution with light petroleum (300 ml.) gave, from aqueous acetic acid–methanol, *iso*euphadiene (*ca.* 1 g.). Recrystallised from methylene dichloride–methanol this had m. p. 64—66°, $[\alpha]_D$ −30° (*c*, 1·70) (Found: C, 87·5; H, 12·4. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%).

*iso*Euphadiene (3·0 g.) in methylene dichloride (50 ml.) was treated with ozone at −70° until the appearance of a faint blue colour. Glacial acetic acid (20 ml.) and zinc dust (3·0 g.) were added with stirring, and the stirring was continued for 3 hr. at 0—10°. The methylene dichloride was distilled over into 2 : 4-dinitrophenylhydrazine hydrochloride solution. The precipitate of acetone 2 : 4-dinitrophenylhydrazone (10%) was identified by m. p. and mixed m. p. (126°).

Dehydrogenation of iso*Euphadiene.*—*iso*Euphadiene (12 g.) and selenium powder (24 g.) were heated together at 350° for 48 hr The product was worked up as described above for the dehydrogenation of euphadiene. Chromatography over alumina and elution with light petroleum (250-ml. portions) gave: (i) an oil (1·5 g.), (ii) a solid (25 mg.), m. p. 82—92°, (iii) a solid (25 mg.), m. p. 100—106°, (iv) a trace of oil, and (v) a solid (25 mg.), m. p. 220—235°. Distillation of fraction (i) gave an oil, b. p. 100—120°/2 mm. Dissolution in ethanol and addition of picric acid gave 1 : 2 : 5-trimethylnaphthalene picrate, m. p. 133—135°. Recrystallisation from ethanol furnished pure material (140 mg.), m. p. and mixed m. p. 139—140° (Found: C, 57·0; H, 4·5; N, 11·4. Calc. for $C_{19}H_{17}O_7N_3$: C, 57·15; H, 4·5; N, 10·5%). The picrate was decomposed to give 1 : 2 : 5-trimethylnaphthalene, identified by m. p., mixed m. p., and absorption spectrum ($\lambda_{max.}$ 230, 278, 289, and 324 mμ, $\varepsilon_{max.}$ 115,000, 7500, 8600, and 1500). The authentic specimens of 1 : 2 : 5-trimethylnaphthalene and its picrate were kindly supplied by Professor Sir Ian Heilbron, D.S.O., F.R.S., to whom we express our best thanks. Examination of fractions (ii), (iii), and (v) gave no indication of 1 : 7 : 8-trimethylphenanthrene.

Bromination of the Diketone (XXIII; R = OAc, R′ = C_8H_{17}).—The bromination experiments were carried out as detailed by Barnes, Barton, Cole, Fawcett, and Thomas (*J.*, 1953, 571) except that the concentration of bromine was approx. 2 g. per 100 ml. of acetic acid. (The figure of 19 g. per 100 ml. of acetic acid given in that paper should read 1·9 g.) The product (100 mg.) from the bromination of the diketone in acetic acid (100 ml.) was refluxed with zinc dust (5 g.; added portionwise) for 2 hr. Crystallisation from methanol gave back the parent acetoxy-diketone (XXIII; R = OAc, R′ = C_8H_{17}) (m. p. and mixed m. p.).

Dehydrogenation of iso*Euphenyl Acetate with Selenium Dioxide.*—*iso*Euphenyl acetate (500 mg.) in acetic acid (45 ml.) was heated under reflux with selenium dioxide (250 mg.) in the minimum of water for 3 hr. Chromatography of the product over alumina and elution with 1 : 3 benzene–light petroleum gave (from methanol) *iso*euphadienyl acetate, m. p. 92—94°, $[\alpha]_D$ +18° (*c*, 0·4), $\lambda_{max.}$ 246, 255, and 264 mμ (log ε 4·25, 4·35, and 4·15 respectively), undepressed in m. p. on admixture with an authentic specimen with the same constants prepared from *iso*euphenyl acetate oxide (Vilkas, *Bull. Soc. chim. France*, 1950, 582) (Found: C, 81·9; H, 11·4. Calc. for $C_{32}H_{50}O_2$: C, 82·0; H, 11·15%).

Hydrogenation of iso*Euphadienyl Acetate.*—*iso*Euphadienyl acetate, m. p. 90—92°, $[\alpha]_D$ +18° (*c*, 1·70) (200 mg.), in glacial acetic acid (20 ml.) was hydrogenated over platinum at 80° for 1 hr. Crystallisation of the product from absolute ethanol gave *iso*euphenyl acetate (140 mg.), m. p. 110—111°, $[\alpha]_D$ −9·0° (*c*, 2·3), undepressed in m. p. on admixture with an authentic specimen of m. p. 110—112°.

The hydrogenation product (120 mg.) was hydrolysed with lithium aluminium hydride (excess) in ether (40 ml.). Crystallisation of the product from nitromethane gave *iso*euphenol, m. p. and mixed m. p. 98—100°, $[\alpha]_D$ −17° (*c*, 2·55).

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Acylation and Allied Reactions Catalysed by Strong Acids. Part XIII. The Isomeric* p-*Tolyl Xylyl Sulphones.*

By H. Burton and P. F. G. Praill.

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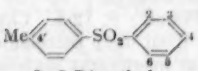
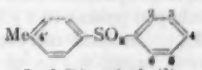
The action of toluene-*p*-sulphonyl perchlorate on the xylenes is investigated with reference to the possible formation of xylyl toluene-*p*-sulphinates as by-products accompanying the *p*-tolyl xylyl sulphones. The results are not conclusive. It has been found that toluene-*p*-sulphonyl chloride, *m*-xylene, and aluminium chloride in the absence of a solvent give a product which yields some toluene-*p*-sulphinic acid on alkaline hydrolysis.

In the course of some experiments on sulphonyl perchlorates (Burton and Hopkins, *J.*, 1952, 4457) it was shown that the properties of *p*-tolyl *m*-4-xylyl sulphone did not agree with those previously reported by Meyer (*Annalen*, 1923, **433**, 343). The possibility that the *m*-xylene used by Meyer was not pure, was put forward. Since the isomeric sulphones from *o*- and *p*-xylene have not been reported, it seemed worthwhile to prepare them. The orientation of these compounds has not been rigidly established but they have been allotted the structures that would normally be predicted for them.

By Meyer's procedure with toluene-*p*-sulphonyl chloride and aluminium chloride, *p*-xylene gave an almost quantitative yield of *p*-tolyl *p*-2-xylyl sulphone, whilst *o*-xylene gave a mixture of isomeric compounds containing a higher proportion of *p*-tolyl *o*-4-xylyl sulphone. The melting points of these sulphones are listed for comparison:



	M. p.
2 : 3-Dimethyl-	135°
2 : 4-Dimethyl-	51—52
2 : 5-Dimethyl-	109



	M. p.
2 : 6-Dimethyl- (?)	121—122° (Meyer's compound)
3 : 4-Dimethyl-	131—132

Experiments were also carried out with the toluene-*p*-sulphonyl chloride–silver perchlorate mixtures. *p*-Xylene gave, as expected, a reasonable yield (*ca.* 70%) of almost pure *p*-tolyl *p*-2-xylyl sulphone after 24 hours at room temperature. *o*-Xylene under similar conditions gave a somewhat lower yield (56%) of a mixture of isomeric sulphones. This mixture appeared to contain rather more of the *p*-tolyl *o*-3-xylyl sulphone which, nevertheless, was formed in relatively small amount.

Burton and Hopkins (*loc. cit.*) also carried out some preliminary work on the small amounts of secondary products that accompany the sulphones in the sulphonyl perchlorate experiments. These secondary products were shown to be an acidic substance and some phenolic material, both of which could have arisen by the hydrolysis of an ester. It was suggested that this ester could have arisen by the direct attack of the sulphonyl cation on the aromatic component through the oxygen, thus leading to an aryl sulphinate, Ar·O·SO·R.

In a further attempt to identify these by-products we have studied the alkali-soluble material resulting from the treatment of the crude reaction product with potassium hydroxide in alcohol (or in dioxan). In the experiments with *m*-xylene and aluminium chloride, especially in the absence of solvent, it has been found that the alkali-soluble material contains toluene-*p*-sulphinic acid, identified by its ready addition to *p*-benzoquinone to form 2 : 5-dihydroxy-4′-methyldiphenyl sulphone. In no case was any phenolic material observed, but traces of thiocresol appear to have been formed. The mechanism of the reduction process by which these compounds have been produced has not been determined, but it is probable that the trace of thiocresol arises by the well-known conversion of a sulphinic acid into a sulphonic acid and thiolsulphonate.

The hydrolysis products from the perchlorate experiments yielded small amounts of

* Part XII, *J.*, 1954, 1456.

resinous materials that had a strong phenolic smell. These were soluble in sodium hydroxide solution but not in sodium hydrogen carbonate. No positive colour reaction was obtained with ferric chloride. Attempts to isolate bromo-derivatives, phenylcarbamates, or 1-naphthylcarbamates from this fraction were unsuccessful. Traces of derivatives were occasionally obtained but these appeared to be mixtures. The small amount of acidic substance arising from the hydrolysis did not give identifiable amounts of 2 : 5-dihydroxy-4'-methyldiphenyl sulphone, nor a benzylthiuronium salt. However, the concentrate from an ethereal solution of the acid turned dark blue on keeping, as did a sample of *p*-toluenesulphinic acid.

Thus, while evidence for the formation of traces of toluenesulphinic esters has been obtained, it has not been possible to ascertain the exact constitution of these compounds.

Experimental

Materials.—Silver perchlorate was treated as before; aluminium chloride (laboratory reagent) was freshly powdered lump. Other reagents were dried and redistilled. *o*- and *m*-Xylene had b. p. 144° and 137—138°, respectively; *p*-xylene had m. p. 13—14°.

Reactions with m-*Xylene.—Method* (*A*). (i) Toluene-*p*-sulphonyl chloride (0·053 mole) was added all at once to a mixture of *m*-xylene (0·05 mole) and powdered aluminium chloride (0·082 mole). After a short induction period there was copious evolution of hydrogen chloride. The temperature rose to 30—40° and the mixture became almost homogeneous. After 30—45 min. it was heated to 40—50° for 30 min.; it became deep mauve. The cooled mixture was decomposed by 16% hydrochloric acid (50 ml.) and heating under reflux for 2—3 hr. The mixture was then steam-distilled until the distillate was clear. The gummy product failed to crystallise on cooling or on being seeded.

The gum was dried in a vacuum-desiccator (P_2O_5) and then dissolved in ether. After 2 months, the crystals that had separated were recrystallised from light petroleum (b. p. 60—80°). The colourless diamond-shaped prisms (0·2 g.) gave a clear melt by 74° (Found : S, 12·4. Calc. for $C_{15}H_{16}O_2S$: S, 12·3%). Several recrystallisations of this material from light petroleum, or light petroleum–ethanol, raised the m. p. to 110—112°, but there was insufficient material for a satisfactory analysis.

When the bulk of the material was kept for several months in a refrigerator, some large colourless prisms separated which, when washed free from gummy material, melted at 50—51°.

(ii) A similar reaction was carried out in nitrobenzene (27 ml.) with 0·025 mole of *m*-xylene. The mixture was heated at 80—90° for 4 hr. The crude product, which almost completely solidified on drying in the desiccator, was extracted with boiling light petroleum (b. p. 60—80°) to separate it from a little resinous material. The slightly brown crystalline product (4·1 g., 0·016 mole), m. p. 49—50°, crystallised from light petroleum as colourless prisms, m. p. 51—52° (Found : C, 69·2; H, 6·2; S, 12·6. Calc. for $C_{15}H_{16}O_2S$: C, 69·2; H, 6·2; S, 12·3%).

In subsequent experiments the boiling with hydrochloric acid and the steam-distillation were omitted. Instead, the crude gum was taken up in ether, and the solution was washed free from acid, dried (Na_2SO_4), and evaporated to dryness. The residual gum (*ca.* 11 g.) was boiled with excess of alcoholic potassium hydroxide for 2 hr. and the cooled solution was poured into 3—4 volumes of water. The oily material was again taken up in ether, and the ethereal solution washed with water and dried (Na_2SO_4). Evaporation of the ethereal solution gave a gum which proved to be as resistant to crystallisation as in earlier experiments.

The gum distilled at 174—175°/1·3 × 10^{-3} mm.; the colourless distillate slowly crystallised to a slightly sticky solid, m. p. and mixed m. p. 42—43°. No separation of an impurity could be effected by chromatographic adsorption on an alumina column, ethanol being used as an eluant.

The alkaline washings from the hydrolysis were acidified with sulphuric acid (Congo-red), and extracted several times with small amounts of ether. The combined ethereal extracts were washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to dryness. Small amounts of gum were obtained which had a smell resembling that of thiocresol.

The sodium hydrogen carbonate washings were warmed to remove dissolved ether and acidified with dilute sulphuric acid. A saturated aqueous solution of *p*-benzoquinone was added, and the mixture left at 0° for several hours. The light brown solid that separated (*ca.* 0·1 g.) melted at 209—210° (mixed m. p. with 2 : 5-dihydroxy-4'-methyldiphenyl sulphone, 209—210°) (Borsche and Frank, *Annalen*, **1926**, **450**, 75, give m. p. 211°) (Found : S, 11·6. Calc. for $C_{13}H_{12}O_4S$: S, 12·1%).

(iii) Another experiment was carried out with five times the original quantities. The main product was the low-melting *p*-tolyl *m*-4-xylyl sulphone, m. p. 51—52°, but repeated recrystallisation of the solid which separated first from the mixture gave material (0·51 g.) of m. p. 74—75°.

Attempted purification of this material by adsorption from benzene–light petroleum (b. p. 60—80°) (1 : 1) on an alumina column (16 × 1·5 cm.). and elution with ethanol, effected little change.

Five more recrystallisations from light petroleum gave colourless, diamond-shaped prisms (25 mg.), m. p. 120—121° (Found: C, 69·7; H, 5·8; S, 11·9. Calc. for $C_{15}H_{16}O_2S$: C, 69·2; H, 6·2; S, 12·3%) (Meyer, *loc. cit.*, reported m. p. 120—121° for *p*-tolyl *m*-4-xylyl sulphone).

Method (*B*). Toluene-*p*-sulphonyl chloride (0·05 mole) in nitromethane (20·0 g.) was added during 16—17 min. to a solution of silver perchlorate (0·05 mole) in *m*-xylene (0·27 mole) and nitromethane (53·5 g.). The temperature of the mixture rose to 25°. After 24 hr. at room temperature the mixture was filtered on to crushed ice. Recovery of silver chloride was 94% of the theoretical amount.

The mixture was then taken up in ether as in method (A). All nitromethane was removed from the reaction product (11·7 g.) before treating it with alcoholic potassium hydroxide. Alkaline washings from the hydrolysis yielded small amounts (0·1—0·2 g.) of a brown resin which had a phenolic smell: it was insoluble in sodium hydrogen carbonate solution. The dried residue was treated with phenyl *iso*cyanate (or 1-naphthyl *iso*cyanate) in sodium-dried light petroleum (b. p. 80—100°); little reaction occurred on warming even in the presence of a drop of triethylamine. Any substituted urea was removed from the mixture; the petroleum solution sometimes deposited traces of crystalline material.

The phenylcarbamate melted over a range, 70—80°, but did not depress the m. p. of the phenylcarbamate of *m*-4-xylenol, m. p. 102° (Heilbron's " Dictionary of Organic Compounds " gives m. p. 102°).

Reactions with o-*Xylene.—Method* (*A*). *o*-Xylene (0·05 mole) reacted with toluene-*p*-sulphonyl chloride (0·053 mole) and aluminium chloride (0·082 mole) under the conditions used for *m*-xylene. The crude sulphone (11·8 g.), recrystallised from ethyl alcohol and then from benzene–light petroleum, gave colourless flaky needles, m. p. 131—132° (Found: C, 69·0; H, 6·1; S, 12·5. $C_{15}H_{16}O_2S$ requires C, 69·2; H, 6·2; S, 12·3%). This material, which was the major product, was probably p-*tolyl o*-4-*xylyl sulphone*.

The alcoholic mother-liquors slowly deposited a few long needles. On repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) colourless prisms of (probably) p-*tolyl* o-3-*xylyl sulphone*, m. p. 135°, were obtained (Found: C, 69·3; H, 6·3; S, 12·4%). On admixture with the main product the m. p. was 107°.

Method (*B*). An experiment using silver perchlorate, carried out in the same way as for *m*-xylene, gave material (7·3 g.) of m. p. 107°. Slow crystallisation from benzene–light petroleum gave long colourless prisms (0·84 g.) and clusters of fine needles. The prisms were separated by hand picking and were recrystallised to constant m. p. (135°). This was unchanged by adsorption from a benzene solution on an aluminia column (16 × 1·5 cm.) followed by elution with ethyl alcohol. The m. p. with the higher-melting material from method (A) was 135°. Chromatographic treatment of the remaining crystalline material did not effect complete separation but the product was mainly *p*-tolyl *o*-4-xylyl sulphone (mixed m. p.).

A small amount of phenolic by-product was obtained from this experiment but no derivative of known constitution was obtained.

Reactions with p-*Xylene.—Method* (*A*). This method, carried out as for the other xylenes, gave an almost quantitative yield (12·0 g.) of nearly pure p-*tolyl* p-*xylyl sulphone*, m. p. 105—106°. Recrystallisation from 96% ethyl alcohol gave clusters of colourless prisms, m. p. 109° (Found: C, 69·2; H, 6·0; S, 12·3%).

Method (*B*). The silver perchlorate technique being used, the crude product (11·0 g.) melted at 108—109° after one crystallisation from ethanol.

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Aryl-2-halogenoalkylamines. Part XIII. Chloroethylamino-derivatives of Some Phenoxyalkanoic Acids and of Some Substituted α-Amino-acids.*

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[Reprint Order No. 5892.]

The compounds $(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot O\cdot [CH_2]_n\cdot CO_2H$, where $n = 1$—4, and $(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot [CH_2]_n\cdot CH(NH_2)\cdot CO_2H$, where $n = 0$, 2, and 3, have been prepared, and the reactivities of their chlorine atoms have been assessed by determining the rates of hydrolysis in aqueous acetone. The tumour-growth inhibitory activity of a number of derivatives is briefly discussed.

In continuation of the programme outlined in Part XII,* namely, the preparation of compounds having a more selective action on neoplastic tissues, further derivatives of the "aromatic nitrogen mustard," *NN*-di-2-chloroethylaniline, have been prepared. The preparation and properties of some new carboxy-substituted derivatives and of some related α-amino-acids are described in the present communication.

The four *p*-di-2-chloroethylaminophenoxy-acids (I; $R = CH_2\cdot CH_2Cl$, $R' = H$; $n = 1$—4) were prepared by hydroxyethylation of the appropriate aminoester (I; R = H, R′ = Me or Et) by reaction with an excess of ethylene oxide in aqueous acetic acid followed by conversion of the hydroxyethyl ester into the dichloro-ester (I; $R = CH_2\cdot CH_2Cl$, R′ = Me or Et) by treatment with phosphorus oxychloride, and subsequent hydrolysis with concentrated hydrochloric acid (cf. Part XII).

p-Acetamidophenoxyacetic acid was prepared by reaction of *p*-acetamidophenol with chloroacetic acid in alkaline solution (Howard, *Ber.*, 1897, **30**, 546) and contrary to the experience of Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 2188) it was found possible to prepare β-*p*-acetamidophenoxypropionic acid in a similar manner by using β-bromopropionic acid. Heating these acetamido-acids with alcoholic hydrogen chloride caused esterification and simultaneous removal of the acetyl group.

1 : 3-Dibromopropane condensed with *p*-acetamidophenol to give *p*-acetamidophenoxypropyl bromide which was converted successively into the nitrile and γ-*p*-aminophenoxybutyric acid (I; R = R′ = H, $n = 3$) (Jacobs and Heidelberger, *loc. cit.*).

(I) $p\text{-}R_2N\cdot C_6H_4\cdot O\cdot [CH_2]_n\cdot CO_2R'$ $p\text{-}(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot [CH_2]_n\cdot CO_2H$ (II)

(III) $p\text{-}(Cl\cdot CH_2\cdot CH_2)_2N\cdot C_6H_4\cdot [CH_2]_n\cdot CH(NH_2)\cdot CO_2H$ $p\text{-}O_2N\cdot C_6H_4\cdot [CH_2]_n\cdot C(NHAc)(CO_2Et)_2$ (IV)

(V) $p\text{-}R_2N\cdot C_6H_4\cdot [CH_2]_n\cdot C(NHAc)(CO_2Et)_2$ $O_2N\cdot C_6H_4\cdot [CH_2]_3\cdot \overset{+}{N}C_5H_5)Br^-$ (VI)

δ-*p*-Aminophenoxyvaleric acid (I; R = R′ = H, $n = 4$) was similarly prepared starting from 1 : 4-dibromobutane. The yield of *p*-acetamidophenoxydecyl bromide from 1 : 10-dibromodecane was insufficient for further study.

β-*p*-(Di-2-chloroethylamino)phenylpropionic acid (II; $n = 2$) is a moderately effective cytotoxic agent (Part XII) and recently Bergel and Stock (*J.*, 1954, 2409) have shown that the introduction of an α-amino-group giving the phenylalanine derivative (III; $n = 1$) leads to considerable enhancement of biological activity. γ-*p*-(Di-2-chloroethylamino)-phenylbutyric acid (II; $n = 3$) is a very effective compound and it was thought that the introduction of an α-amino-group into this structure might lead to a corresponding increase in activity. In view of the considerable variation in biological activity encountered in the homologous series (I) and (II) it was of interest to prepare compounds of structure (III) where $n = 0$, 2, and 3.

In exploratory experiments acetamidomalonic ester was condensed with phenethyl bromide in the presence of sodium ethoxide, and hydrolysis of the resulting diethyl *C*-acetamido-*C*-phenethylmalonate gave α-amino-γ-phenylbutyric acid. *p*-Nitrophenylethyl bromide similarly gave α-amino-γ-*p*-nitrophenylbutyric acid. Hydrogenation of the

* Part XII, *J.*, 1953, 2386.

intermediate diethyl acetamido-*p*-nitrophenylethylmalonate over palladium–calcium carbonate gave the corresponding *p*-amino-derivative (V; R = H, $n = 2$) which with ethylene oxide yielded diethyl acetamido-*p*-(di-2-hydroxyethylamino)phenylethylmalonate (V; R = $CH_2 \cdot CH_2 \cdot OH$, $n = 2$). This was converted into the dichloroethyl ester which with hot concentrated hydrochloric acid gave the required α-amino-γ-*p*-(di-2-chloroethylamino)phenylbutyric acid (III; $n = 2$).

Considerable difficulty was encountered in the preparation of *p*-nitrophenylpropyl bromide which was required for the synthesis of the homologue (III; $n = 3$). Leffler and Volwiler (*J. Amer. Chem. Soc.*, 1938, **60**, 896) claim that when phenylpropyl bromide was nitrated by the somewhat ill-defined method used by Braun and Deutsch (*Ber.*, 1912, **45**, 2504) for the corresponding chloride an 82% yield of *p*-nitro-compound was obtained. In our experience all methods of nitration have given approximately equal amounts of *o*- and *p*-isomers and these can only be separated with difficulty by slow fractional distillation. In an attempted chromatographic separation of the isomers on activated alumina considerable amounts of the bromide were converted into the alcohol. The higher-boiling isomer was shown to be *p*-nitrophenylpropyl bromide by the formation of *p*-nitrobenzoic acid when it was oxidised with chromic acid. The *o*- and the *p*-isomer were characterised by the preparation of their respective pyridinium salts (VI).

The oily diethyl acetamido-*p*-(di-2-hydroxyethylamino)phenylpropylmalonate (V; R = $CH_2 \cdot CH_2 \cdot OH$, $n = 3$), which was prepared as above by way of the nitro-diester (IV; $n = 3$) and the amino-diester (V; R = H, $n = 3$), was converted directly into the amorphous di-2-chloroethyl ester (V; R = $Cl \cdot CH_2 \cdot CH_2$, $n = 3$) which on acid hydrolysis gave the crystalline α-amino-δ-*p*-(di-2-chloroethylamino)phenylvaleric acid (III; $n = 3$).

The first member of the series (III; $n = 0$) could not be prepared in the usual manner since *p*-bromonitrobenzene failed to condense with diethyl acetamidomalonate. Another route explored involved the preparation of *p*-aminophenyl-α-hydroxyiminoacetic ester (VII; R = H, X = NH_2). Whilst hydrogenation over Raney nickel of the nitro-oxime (VII; R = H, X = NO_2) effected reduction of both nitro- and hydroxyimino-groups, giving the diamino-ester (VIII; R = Et), hydrogenation over platinum gave the required amino-oxime (VII; R = H, X = NH_2). Acid hydrolysis of the diamino-ester (VIII; R = Et) gave the diamino-acid (VIII; R = H) which had previously been obtained by Grant and Pyman (*J.*, 1921, **119**, 1893).

p-X·C_6H_4·C(:N·OR)·CO_2Et (VII) *p*-NH_2·C_6H_4·CH(NH_2)·CO_2R (VIII) *p*-(Cl·CH_2·CH_2)$_2$N·C_6H_4·CH_2·CO_2Et (IX)

p-(Cl·CH_2·CH_2)$_2$N·C_6H_4·CHO (X) *p*-(Cl·CH_2·CH_2)$_2$N·C_6H_4·CH(NH_2)·CN (XI)

p-(Cl·CH_2·CH_2)$_2$·C_6H_4·O·CH_2·CH_2·C(NHAc)(CO_2Et)$_2$ (XII)

No useful product was obtained by the action of ethylene oxide on the amino-hydroxyimino-ester and it was considered that this might be due to partial reaction with the hydroxyimino-group. Accordingly the *O*-acetate (VII; X = NH_2, R = Ac) was prepared by catalytic hydrogenation of the nitro-*O*-acetate (VII; X = NO_2, R = Ac). The amino-hydroxyimino-ester and its *O*-acetate gave the diacetate (VII; X = NHAc, R = Ac) on treatment with acetic anhydride. It was not possible to obtain the desired hydroxyethylamino-compound by treating the *O*-acetate (VII; X = NH_2, R = Ac) with ethylene oxide.

An attempt to prepare the α-hydroxyimino-derivative from ethyl *p*-(di-2-chloroethylamino)phenyl acetate (IX) was unsuccessful. The required amino-acid was eventually obtained by carrying out a Strecker reaction on *p*-(di-2-chloroethylamino)benzaldehyde (X). The amino-nitrile thus obtained was quantitatively converted into α-amino-*p*-(di-2-chloroethylamino)phenylacetic acid (III; $n = 0$) by heating it with concentrated hydrochloric acid.

p-(Di-2-hydroxyethylamino)phenoxyethyl bromide condensed with acetamidomalonic ester to give a product which was not isolated but was converted directly into acetamido-*p*-(di-2-chloroethylamino)phenoxyethylmalonic ester (XII).

Since a correlation between the chemical reactivity of aryl-2-halogenoalkylamines and their cytotoxic activity has been established (Ross, *Adv. Cancer Res.*, 1953, **1**, 397) the rates of hydrolysis of a number of the new compounds under standard conditions have been determined (cf. Ross, *J.*, 1949, 183, and subsequent papers). The annexed Table also indicates the effectiveness of the compounds as inhibitors of the growth of the transplanted

The extent of hydrolysis of 2-chloroethylamino-acids in 50% acetone at 66°. Concn. of amino-acid derivative 0·02M. Time, 30 min.

	Free acid	Ester	Sodium salt				Free acid	Ester	Sodium salt		
	H or Cl	H or Cl					H or Cl	H or Cl			
n	(%)	(%)	H (%)	Cl (%)	Biological activity †	*n*	(%)	(%)	H (%)	Cl (%)	Biological activity †
	p-(Cl·CH$_2$·CH$_2$)$_2$N·C$_6$H$_4$·O·[CH$_2$]$_n$·CO$_2$H						*p*-(Cl·CH$_2$·CH$_2$)$_2$N·C$_6$H$_4$·[CH$_2$]$_n$·CH(NH$_2$)·CO$_2$H				
1	53	44	52	68	+	0	10	—	—	—	‡
2	57	—	52	70	+++	1 *	22	—	—	—	+++
3	62	63	52	71	++	2	30	—	—	—	+++
4	64	—	54	70	+++	3	34	—	—	—	+++

* Bergel and Stock, *J.*, 1954, 2409; see also British Empire Cancer Campaign Report for 1953, p. 6.
† As inhibitors of the growth of the transplanted Walker rat carcinoma.
‡ Still under test.

Walker rat carcinoma (for techniques see Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255; Haddow, Harris, Kon, and Roe, *Phil. Trans. Roy. Soc.*, 1948, *A*, **241**, 147).

Biological Results (Personal communication from Professor A. Haddow).—All four acids (I; $n = 1$—4) exhibit tumour-growth inhibitory activity, and of these the phenoxypropionic acid derivative (I; $n = 2$) is outstanding. It is interesting that this compound is isosteric with the most active member of the series (II), namely, the phenylbutyric acid derivative ($n = 3$) (Part XII). This supports the view expressed there that the especial activity of the phenylbutyric acid derivative was connected with its molecular structure. Activity in these compounds is still dependent on the reactive chlorine atoms since *p*-aminophenylbutyric acid and its *NN*-di-2-hydroxyethyl derivative are ineffective.

In the series of α-amino-acid derivatives the biological activity of the DL-forms of three members have so far been compared (see, also, Bergel and Stock, *loc. cit.*). Preliminary investigations indicate that the amino-acids (III; $n = 1$—3) are equally effective at a dose level of 1 mg. per rat. It is thus apparent that the insertion of an α-amino-group into the phenylbutyric acid derivative (II; $n = 3$) does not result in an increase in activity of the magnitude encountered by the insertion of such a group into the phenylpropionic acid derivative (II; $n = 2$).

Experimental

p-(*Di-2-chloroethylamino*)*phenoxyacetic Acid*.—Ethylene oxide (25 g.) was added to a stirred suspension of ethyl *p*-aminophenoxyacetate (25 g.) in N-acetic acid (50 ml.). Stirring was continued for 4 hr. and next day the excess of ethylene oxide was removed under reduced pressure and the product was extracted with ether. The ether solution was washed with 2N-sodium hydrogen carbonate and water and then dried and evaporated. *Ethyl* p-(*di-2-hydroxyethylamino*)*phenoxyacetate* (18 g.) formed prisms, m. p. 57·5°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 59·3; H, 7·6. $C_{14}H_{21}O_5N$ requires C, 59·3; H, 7·5%). This ethyl ester was converted into *ethyl* p-(*di-2-chloroethylamino*)*phenoxyacetate*, rhombs, m. p. 55·5°, from light petroleum (b. p. 40—60°) (Found: C, 52·9; H, 6·2. $C_{14}H_{19}O_3NCl_2$ requires C, 52·5; H, 6·0%), and p-(*di-2-chloroethylamino*)*phenoxyacetic acid*, needles, m. p. 112°, from *cyclo*hexane (Found: C, 49·4; H, 5·4. $C_{12}H_{15}O_3NCl$ requires C, 49·3; H, 5·2%), by methods described in Part XII.

Methyl β-p-(*di-2-hydroxyethylamino*)*phenoxypropionate*, needles, m. p. 68°, from benzene (Found: C, 58·9; H, 7·5. $C_{14}H_{21}O_5N$ requires C, 59·3; H, 7·5%), *methyl* β-p-(*di-2-chloroethylamino*)*phenoxypropionate*, rhombs, m. p. 51°, from pentane (Found: C, 52·3; H, 6·2. $C_{14}H_{19}O_3NCl$ requires C, 52·5; H, 6·0%), β-p-(*di-2-chloroethylamino*)*phenoxypropionic acid*,

needles, m. p. 93°, from *cyclo*hexane (Found : C, 51·2; H, 5·9. $C_{13}H_{17}O_3NCl_2$ requires C, 51·0; H, 5·6%), *methyl* γ-p-(*di-2-hydroxyethylamino*)*phenoxybutyrate*, rhombs, m. p. 37°, from benzene–*cyclo*hexane (Found : C, 61·0; H, 7·7. $C_{15}H_{23}O_5N$ requires C, 60·6; H, 7·8%), *methyl* γ-p-(*di-2-chloroethylamino*)*phenoxybutyrate*, small prisms, m. p. 65°, from carbon tetrachloride–light petroleum (b. p. 40—60°) (Found : C, 54·6; H, 6·3. $C_{15}H_{21}O_3NCl_2$ requires C, 53·9; H, 6·3%), and γ-p-(*di-2-chloroethylamino*)*phenoxybutyric acid*, needles, m. p. 85·5°, from *cyclo*hexane (Found : C, 52·8; H, 6·2. $C_{14}H_{19}O_3NCl_2$ requires C, 52·5; H, 6·0%), were similarly prepared from the appropriate amino-ester.

δ-p-(*Di-2-chloroethylamino*)*phenoxyvaleric Acid*.—1 : 4-Dibromobutane (Wilson, *J.*, **1945**, 48) was condensed with *p*-acetamidophenol (40 g.) giving p-*acetamidophenoxybutyl bromide* (42 g.), m. p. 102·5°, flattened needles from carbon tetrachloride (Found : C, 50·8; H, 5·8. $C_{12}H_{16}O_2NBr$ requires C, 50·4; H, 5·6%), which was converted into p-*acetamidophenoxybutyl cyanide* (89%), small prisms, m. p. 105·5°, from benzene (Found : C, 66·7; H, 7·0. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9%) (cf. Jacobs and Heidelberger, *loc. cit.*). Heating the nitrile with concentrated hydrochloric acid gave δ-p-*aminophenoxyvaleric acid hydrochloride*, rhombs, m. p. 188° (decomp.), from concentrated hydrochloric acid (Found : C, 53·5; H, 6·6. $C_{11}H_{16}O_3NCl$ requires C, 53·8; H, 6·6%). *Methyl* δ-p-*aminophenoxyvalerate*, platelets, m. p. 65°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 64·4; H, 7·7. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·7%), was converted into the *NN*-di-2-hydroxyethyl and *NN*-di-2-chloroethyl derivatives in the usual manner and as these did not crystallise the latter was hydrolysed to δ-p-(*di-2-chloroethylamino*)*phenoxyvaleric acid*, needles, m. p. 87·5°, from light petroleum (b. p. 60—80°) (Found : C, 53·8; H, 6·7. $C_{15}H_{21}O_3NCl_2$ requires C, 53·9; H, 6·3%).

p-*Acetamidophenoxydecyl Bromide*.—Decamethylene dibromide (30 g.) and *p*-acetamidophenol (5 g.) were heated under reflux in a solution of sodium hydroxide (1·33 g.) in ethanol (30 ml.) and water (1·5 ml.). After 4 hr. the mixture was steam-distilled to remove unchanged dibromide. The non-volatile material was dissolved in benzene–light petroleum (b. p. 60—80°) (1 : 1), and the solution was passed through a short column of activated alumina. The eluates contained a very small amount of the *phenoxydecyl bromide* which formed small prisms, m. p. 122·5—125°, from pentane (Found : C, 58·9; H, 8·0; N, 3·7. $C_{18}H_{28}O_2NBr$ requires C, 58·4; H, 7·6; N, 3·8%).

Diethyl Acetamidophenylethylmalonate.—Diethyl acetamidomalonate (5·4 g.) was added to a solution prepared by dissolving sodium (0·6 g.) in ethanol (50 ml.). After the further addition of phenethyl bromide (6 g.) the mixture was heated under reflux with stirring for 16 hr. The filtered solution was evaporated under reduced pressure and a solution of the resulting oil in benzene was washed with water, then dried and evaporated. *Diethyl* C-*acetamido*-C-*phenethylmalonate* (5·1 g.) formed needles, m. p. 114—115°, from light petroleum (b. p. 60—80°) (Found : C, 63·5; H, 7·3. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·2%). When this ester (1 g.) was heated for 3 hr. in 3N-hydrochloric acid and then sodium acetate was added to the concentrated solution α-amino-γ-phenylbutyric acid separated as prisms, m. p. 295—296° (cf. Knoop and Hoessli, *Ber.*, 1906, **39**, 1478).

Diethyl Acetamido-p-*nitrophenylethylmalonate*.—The p-*nitro-ester* (39 g.), prepared in a similar manner by condensing *p*-nitrophenylethyl bromide (40 g.) (Foreman and McElvain, *J. Amer. Chem. Soc.*, 1940, **62**, 1436) with acetamidomalonic ester (33·2 g.), formed fine needles, m. p. 117·5°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 55·9; H, 6·2; N, 7·6. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·1; N, 7·7%). On hydrolysis with 3N-hydrochloric acid the *p*-nitro-ester yielded *α-amino-γ-p-nitrophenylbutyric acid*, pale yellow needles, m. p. 233°, from water (Found : C, 53·6; H, 5·7; N, 12·3. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). Potentiometric titration of this acid in aqueous solution indicated that the pK_a of the amino-group was 9·1 and that of the carboxyl group was 3·05.

Diethyl Acetamido-p-*aminophenylethylmalonate*.—The *p*-nitro-ester (30 g.), dissolved in ethanol (500 ml.) containing Raney nickel catalyst, was shaken at 40—50° in hydrogen until the theoretical amount had been taken up. The p-*amino-ester* formed small prisms, m. p. 113°, from benzene–*cyclo*hexane (Found : C, 60·6; H, 7·3; N, 8·7. $C_{17}H_{24}O_5N_2$ requires C, 60·7; H, 7·2; N, 8·3%).

Diethyl Acetamido-p-(*di-2-chloroethylamino*)*phenylethylmalonate*.—The *p*-amino-ester was treated with ethylene oxide in 2N-acetic acid in the usual manner. *Diethyl acetamido*-p-(*di-2-hydroxyethylamino*)*phenylethylmalonate* formed small prisms, m. p. 122°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 59·1; H, 7·4; N, 6·4. $C_{21}H_{32}O_7N_2$ requires C, 59·4; H, 7·6; N, 6·6%). When this dihydroxyethyl ester (0·7 g.) was heated with phosphorus oxychloride (1 ml.) in dry benzene (10 ml.) for 0·5 hr., the corresponding *di-2-chloroethyl derivative*,

small needles, m. p. 79—80°, from light petroleum (b. p. 60—80°), was obtained (Found: C, 54·7; H, 6·6; N, 6·1. $C_{21}H_{29}O_5N_2Cl_3$ requires C, 54·7; H, 6·6; N, 6·1%).

α-Amino-γ-p-(di-2-chloroethylamino)phenylbutyric Acid.—Heating the di-2-chloroethyl ester under reflux with concentrated hydrochloric acid for 1 hr. caused hydrolysis and decarboxylation, with the formation of the *α-aminobutyric acid*, small prisms, m. p. 174—176°, from ethanol (Found: C, 52·6; H, 6·9; N, 8·6. $C_{14}H_{20}O_2N_2Cl_2$ requires C, 52·7; H, 6·3; N, 8·8%).

p-(*Di-2-hydroxyethylamino*)*phenoxyethyl Bromide.*—To *p*-aminophenoxyethyl bromide (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2442) (5·0 g.) in 2N-acetic acid (15 ml.), ethylene oxide (20 ml.) was added and the mixture was stirred for 4 hr. The *dihydroxyethylamino*-compound formed prisms, m. p. 82—83°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 47·5; H, 6·2; Br, 26·2. $C_{12}H_{18}O_3NBr$ requires C, 47·4; H, 6·0; Br, 26·3%); it gave a *picrate*, prisms, m. p. 110°, from benzene (Found: C, 41·0; H, 4·25; N, 10·4. $C_{18}H_{21}O_{10}N_4Br$ requires C, 40·5; H, 4·0; N, 10·5%).

Diethyl Acetamido-p-(*di-2-chloroethylamino*)*phenoxyethylmalonate.*—*p*-(Di-2-hydroxyethylamino)phenoxyethyl bromide (9·0 g.) was condensed with acetamidomalonic ester (5·4 g.) as described above. The oily product (10 g.) was heated with phosphorus oxychloride (10 ml.) in benzene (30 ml.) for 1 hr. The benzene solution was poured on ice and then dried and passed through a column of activated alumina. Final elution of the column with ether afforded *diethyl acetamido*-p-(*di-2-chloroethylamino*)*phenoxyethylmalonate* which formed needles, m. p. 102—103°, from light petroleum (b. p. 60—80°) (Found: C, 52·4; H, 6·3; N, 6·2; Cl, 14·4. $C_{21}H_{30}O_6N_2Cl_2$ requires C, 52·8; H, 6·3; N, 5·9; Cl, 14·9%).

3-p-*Nitrophenylpropyl Bromide.*—3-Phenylpropyl bromide (100 g.) was added during 45 min. to a stirred mixture of nitric acid (200 ml.; *d* 1·42) and nitric acid (50 ml.; *d* 1·50). The temperature was kept at 0° during the addition and for a further 2 hr., after which the mixture was poured on crushed ice (1 kg.) and extracted with ether (2·5 l.). The ether layer was washed with an excess of saturated aqueous sodium hydrogen carbonate and finally dried ($CaCl_2$). The yellow oil which remained after evaporation of the ether was slowly distilled at 0·75 mm., the following fractions being collected: (*a*) b. p. 65—70° (37 g. of unchanged bromide), (*b*) b. p. 120—125°, n_D^{23} 1·5691 (4·6 g.), (*c*) b. p. 125—128°, n_D^{23} 1·5732 (18 g.), (*d*) b. p. 128—132°, n_D^{23} 1·5745 (14 g.), (*e*) b. p. 132—134°, n_D^{23} 1·5760 (11 g.), (*f*) b. p. 134—136°, n_D^{23} 1·5775 (6 g.), (*g*) b. p. 136—138°, n_D^{23} 1·5780 (5 g.), and (*h*) b. p. 138—140°, n_D^{23} 1·5792 (20 g.). Fraction (*h*) was pure *p*-nitrophenylpropyl bromide, m. p. −2° to 0°, b. p. 130—136°/0·4 mm., 156—160°/2 mm., n_D^{21} 1·5780 (Leffler and Volwiler, *loc. cit.*, gave b. p. 152—156°/2 mm., n_D^{20} 1·576), which gave *p*-nitrobenzoic acid in high yield on oxidation with chromic–sulphuric acid. When the *p*-nitrobromide was heated with pyridine for 10 min. 1-p-*nitrophenylpropylpyridinium bromide*, prisms from ether–methanol, m. p. 177—180° (Found: C, 52·0; H, 4·7; N, 8·85. $C_{14}H_{15}O_2N_2Br$ requires C, 52·0; H, 4·7; N, 8·7%), was formed. On redistillation fractions (*b*), (*c*), and (*d*) gave *o*-nitrophenylpropyl bromide, m. p. 0°, b. p. 114°/0·75 mm., 138—144°/2 mm., n_D^{21} 1·573, which was characterised by the preparation of its *pyridinium salt*, small prisms, m. p. 182—184°, from ether–methanol, depressed to 150° on admixture with the *p*-isomer (Found: C, 52·1; H, 4·8; N, 8·6%). The *o*-derivative gave no nitrobenzoic acid on oxidation with chromic–sulphuric acid.

α-Amino-δ-p-(di-2-chloroethylamino)phenylvaleric Acid.—*p*-Nitrophenylpropyl bromide was condensed with acetamidomalonic ester by the method described above, to give *diethyl acetamido-p-nitrophenylpropylmalonate*, m. p. 75—78°, fine needles from benzene–light petroleum (b. p. 60—80°) (Found: C, 57·0; H, 6·3. $C_{18}H_{24}O_7N_2$ requires C, 56·8; H, 6·4%). On hydrogenation in ethanol solution over palladium–calcium carbonate the nitro-ester (9·8 g.) gave *diethyl acetamido-p-aminophenylpropylmalonate* (8 g.), m. p. 74—75·5°, prismatic needles from ether–pentane or benzene–*cyclo*hexane (Found: C, 61·9; H, 7·6. $C_{18}H_{26}O_5N_2$ requires C, 61·7; H, 7·5%); it formed a *picrate*, m. p. 179—180°, prisms from benzene (Found: C, 49·8; H, 5·4. $C_{24}H_{29}O_{12}N_5$ requires C, 49·7; H, 5·0%). The amino-ester (6 g.) was treated with ethylene oxide in dilute acetic acid as described above, and the oily product was dissolved in dry chloroform (30 ml.). After addition of phosphorus oxychloride (10 ml.) the solution was heated under reflux for 0·5 hr. and then evaporated under reduced pressure. The residue was dissolved in concentrated hydrochloric acid (50 ml.) and the solution was heated under reflux for 4 hr. On the addition of saturated aqueous ammonium acetate to the ice-cooled solution a buff-coloured precipitate formed. This was collected, washed with ammonium acetate solution, then with water, and dried on porous tile (yield, 3·7 g.). The *amino-acid* was crystallised by dissolution in acetic acid (4 ml. per g.) followed by the addition of benzene (20 ml. per g.), small flattened needles containing acetic acid of crystallisation being slowly deposited. The acetic

acid was slowly lost on exposure to air; a specimen dried at 80°/5 mm. for 3 hr. had m. p. 180—184° (decomp.; dependent on the rate of heating) (Found: C, 54·0; H, 6·6; N, 8·4; Cl, 21·0. $C_{15}H_{22}O_3N_2Cl_2$ requires C, 54·1; H, 6·7; N, 8·4; Cl, 21·3%).

*α-Amino-*p*-(di-2-chloroethylamino)phenylacetic Acid.*—Potassium cyanide (2 g.) and ammonium chloride (1·6 g.) were dissolved in the minimum quantity of water and added to a solution of *p*-(di-2-chloroethylamino)benzaldehyde (2·5 g.) (Anker and Cook, *J.*, 1944, 489) in methanol (50 ml.). After 2 days at room temperature the turbid solution was diluted with water and extracted with ether. The ethereal extract was extracted three times with 2N-hydrochloric acid. The oil which separated from the acid extract on the addition of anhydrous sodium carbonate was dissolved in saturated ethanolic hydrogen chloride and when this was diluted with dry ether small crystals of *α-amino-*p*-(di-2-chloroethylamino)benzyl cyanide dihydrochloride* (1·5 g.), m. p. 110—115° (decomp.), were precipitated (Found: N, 12·6. $C_{12}H_{17}N_3Cl_4$ requires N, 12·2%). A solution of the amino-nitrile hydrochloride (0·5 g.) in concentrated hydrochloric acid (5 ml.) was heated under reflux for 3 hr. On saturation of the cooled solution with sodium acetate *α-amino-*p*-(di-2-chloroethylamino)phenylacetic acid* was precipitated. It formed prisms, m. p. 182°, from methanol (Found: C, 49·2; H, 5·8; N, 9·5; Cl, 24·1. $C_{12}H_{16}O_2N_2Cl_2$ requires C, 49·5; H, 5·5; N, 9·6; Cl, 24·4%).

*Ethyl α-Amino-*p*-aminophenylacetate.*—A solution of α-hydroxyimino-*p*-nitrophenylacetic ester (9 g.) (Borsche, *Ber.*, 1909, **42**, 3597) in methanol (1·5 l.) was hydrogenated over Raney nickel. The filtered solution was concentrated to 200 ml. and saturated with hydrogen chloride, and then dry ether was added. The precipitated *dihydrochloride* (5·35 g.) formed stout prisms, decomp. *ca.* 250°, from ether–methanol (Found: C, 44·4; H, 5·9; N, 10·2; Cl, 26·8. $C_{10}H_{14}O_2N_2,2HCl$ requires C, 44·9; H, 6·0; N, 10·5; Cl, 26·5%). The ester formed a *diacetate*, prisms, m. p. 175—177°, from water (Found: C, 59·9; H, 6·5; N, 10·4. $C_{14}H_{18}O_4N_2$ requires C, 60·4; H, 6·5; N, 10·1%). α-Amino-*p*-aminophenylacetic acid dihydrochloride, which was obtained by heating the diamino-ester (1 g.) with concentrated hydrochloric acid (3 ml.) for 3·5 hr., formed prisms, m. p. >280° from ether–ethanol (Grant and Pyman, *loc. cit.*, record m. p. >280° for this dihydrochloride) (Found: C, 40·4; H, 5·3; N, 11·8. Calc. for $C_8H_{12}O_2N_2Cl_2$: C, 40·2; H, 5·1; N, 11·7%).

Ethyl p*-Aminophenyl-α-hydroxyiminoacetate.*—Ethyl α-hydroxyimino-*p*-nitrophenylacetate (1·7 g.) was hydrogenated over Adams platinum catalyst in methanol (250 ml.). Concentration of the filtered solution gave *ethyl* p*-aminophenyl-α-hydroxyiminoacetate*, which formed prisms, m. p. 141—142°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 57·9; H, 5·9; N, 13·5. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%). The amino-hydroxyimino-ester formed a *hydrochloride*, prisms, m. p. 205°, from ether–ethanol (Found: C, 48·5; H, 5·7; N, 11·4; Cl, 14·9. $C_{10}H_{12}O_3N_2,HCl$ requires C, 49·1; H, 5·4; N, 11·5; Cl, 14·5%), and a *diacetate*, prisms, m. p. 127—128°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 57·8; H, 5·7; N, 9·9. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5; N, 9·6%).

*Ethyl α-Acetoxyimino-*p*-aminophenylacetate.*—Ethyl α-hydroxyimino-*p*-nitrophenylacetate was converted into its O-*acetate*, m. p. 105°, prisms from benzene–light petroleum (b. p. 40—60°) (Found: C, 51·3; H, 4·4; N, 10·3. $C_{12}H_{12}O_6N_2$ requires C, 51·4; H, 4·3; N, 10·0%), by treatment with acetic anhydride, and this acetate afforded *ethyl α-acetoxyimino-*p*-aminophenylacetate*, m. p. 218—219°, prisms from aqueous ethanol (Found: C, 57·2; H, 5·6; N, 11·3. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%), on hydrogenation over a platinum catalyst. The reduction product formed the diacetate, m. p. 127—128°, described above, when treated with acetic anhydride.

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*Hydropteridines. Part III.** 5 : 6 : 7 : 8-*Tetrahydro-4-methylpteridine.*

By P. R. Brook and G. R. Ramage.

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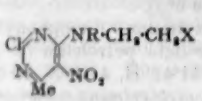
Reduction and simultaneous ring-closure of 4-(*N*-benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl) has made available 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridines (II; R = CH_2Ph, X = H, OH, or Cl). Reduction of the 2-chloro-compound gave 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H).

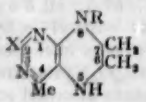
In an attempt to synthesise 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H), Ramage and Trappe (*J.*, 1952, 4410) showed that 4-2′-chloroethylamino-5-nitropyrimidines (*e.g.*, I; R = H, X = Cl) were reasonably stable in the absence from the 2-position of a group capable of initiating tautomerism. Either the introduction of such a group, *e.g.*, hydroxyl in place of the 2-chloro-group in (I; R = H, X = Cl), or reduction of the 5-nitro- to a 5-amino-group, allowed cyclisation involving the pyrimidine nitrogen atom and gave glyoxalinopyrimidines, *i.e.*, (III; X = OH, Y = NO_2; or X = Cl, Y = NH_2 respectively).

4-(*N*-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl) has been prepared, and its reduction and subsequent ring-closure have been studied since the cyclisation to a tetrahydropteridine was expected to be facilitated by the *N*-benzyl group.

2 : 4-Dichloro-6-methyl-5-nitropyrimidine in chloroform was condensed with *N*-benzyl-2-chloroethylamine, the latter being conveniently prepared from 2-benzylaminoethanol by the action of thionyl chloride, rather than hydrochloric acid as used by Goldschmeidt and Jahoda (*Monatsh.*, 1891, **12**, 83). The amine (I; R = CH_2Ph, X = Cl) was obtained as a stable solid which showed no tendency to cyclise in the absence of moisture. Ether, as an alternative solvent in the condensation, gave the same product together with the hydrochloride of the bicyclic compound (IV). It was considered that the latter was formed by cyclisation of the product derived from the amine (I; R = CH_2Ph, X = Cl) by hydrolysis of the reactive 2-chloro-group by moisture in the solvent, and this was supported by its ready formation from the same amine with hydrochloric acid, or with moist ethanol, at the boil. The cyclisation was comparable with that of the non-benzylated compound (I; R = H, X = Cl) (Ramage and Trappe, *loc. cit.*).



(I)



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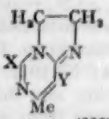

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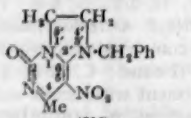

(IV)

Catalytic reduction of the chloro-amine (I; R = CH_2Ph, X = Cl) with Raney nickel in ethanol gave 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = Cl) contaminated with a nickel salt. Cyclisation involving the 5-amino-group must have occurred rapidly after reduction, and the action of the resulting hydrochloride on the catalyst would explain the contamination.

The new mode of cyclisation to a benzyltetrahydropteridine proceeded readily and was evidently favoured by the presence of the benzyl group which removed any possibility of tautomerism. In contrast, the alternative ring closure from the secondary base (I; R = H, X = Cl) leading to a glyoxalinopyrimidine had required refluxing in ethanol (*idem, loc. cit.*).

An alternative route to the pteridine (II; R = CH_2Ph, X = Cl) from the hydroxy-amine (I; R = CH_2Ph, X = OH) was also used. The latter compound was prepared by the condensation of 2-benzylaminoethanol with 2 : 4-dichloro-6-methyl-5-nitropyrimidine, and on reduction with Raney nickel gave 5-amino-4-(*N*-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine, without nickel contamination. Ready cyclisation to the

* Part II, *J.*, 1954, 4109.

pteridine (II; R = CH_2Ph, X = Cl) occurred on treatment with phosphoryl chloride followed by alkali. Hydrogenolysis of the benzyl group in this product was attempted by the use of palladised charcoal in acetic acid (Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984), but only the 2-chloro-group was removed. Treatment with constant-boiling hydrobromic or hydrochloric acid hydrolysed the 2-chloro-group and gave the 2-hydroxypteridine (II; R = CH_2Ph, X = OH). Both the chloro- and the benzyl group were, however, reduced off by sodium in liquid ammonia and 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H) was obtained. 1-Benzylglyoxaline derivatives, which contain a similar " amidine " arrangement of nitrogen atoms, have been debenzylated in this way (Du Vigneaud and Behrens, *J. Biol. Chem.*, 1937, **117**, 27). An attempt merely to effect only debenzylation with a shorter reaction time showed that the chlorine was preferentially attacked, as in hydrogenolysis, and the benzyltetrahydromethylpteridine was again obtained.

5 : 6 : 7 : 8-Tetrahydro-4-methylpteridine was treated with formic acid in the presence of acetic anhydride and gave a monoformyl derivative which, by analogy with the work on reduced pteroylglutamic acid (May, Bardos, Barger, Lansford, Ravel, Sutherland, and Shive, *J. Amer. Chem. Soc.*, 1951, **73**, 3067), was considered to be a 5-formyl derivative. Acylation with acetic formic and diacetic anhydride, however, gave respectively a diformyl and a diacetyl derivative which showed that both the 5- and the 8-position were reactive; so an unambiguous synthesis of the 5-formyl derivative was attempted.

Formylation of the benzylpteridine (II; R = CH_2Ph, X = Cl), in which the 8-position was occupied, definitely established 5-formylation, but treatment of this product with sodium in liquid ammonia caused simultaneous removal of the chloro-, benzyl, and formyl groups, yielding tetrahydro-4-methylpteridine. The formyl group was removed more easily than the benzyl group, since 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = H) was obtained with a shorter reaction time. However, a similar series of reactions *via* the 5-acetyl derivative was successful and gave 5-acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine.

The similarity of the ultra-violet absorption spectrum (cf. Table) of the monoformyl derivative of tetrahydro-4-methylpteridine (II; R = X = H) to that of the 5-acetyl derivative confirmed location of the formyl group also in the 5-position. In addition, the basic strengths of these derivatives and of 4-aminopyrimidine were comparable (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240).

For the diacetyl compound, it was found that the basic strength (cf. Table) was appre-

Basic strengths and ultra-violet absorption spectra.[2]

5 : 6 : 7 : 8-Tetrahydro-4-methylpteridines	pK_a in water and concn. (20°) [1]		$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	$\lambda_{min.}$ (mμ)	log $\varepsilon_{min.}$
(II; R = X = H) ...	—		211, 300	4·18, 3·82	241, 274 *	3·21, 3·68
cation	6·74 (±0·02)	M/100	213, 305	4·12, 3·93	251	3·00
5-Acetyl-8-benzyl- ...	—		217, 263	4·17, 4·11	238, 287 *	3·73, 3·79
cation	5·49 (±0·02) [3]	—	205, 281	4·31, 4·23	245	3·84
8-Benzyl-5-formyl- ...	—		217, 266	4·26, 4·12	240, 290 *	3·79, 3·85
cation	5·46 (± 0·03) [3]	—	207, 282	4·25, 4·22	247	3·70
5-Formyl-	—		216, 253, 288	4·14, 3·93, 3·70	235, 276	3·82, 3·68
cation	5·45 (±0·02)	M/100	211, 272	4·07,4·06	246	3·74
5-Acetyl-	—		217, 248, 287	4·06, 3·94, 3·69	233, 274	3·84, 3·64
cation	5·26 (±0·01)	M/100	210, 271	4·02, 4·01	247	3·76
5 : 8-Diacetyl- [4]	—		219, 241, 265, 284	4·18, 4·02, 3·97, 3·92	233, 260, 277	4·00, 3·97 3·91
cation [5]	2·15 (±0·01)	M/100	—	—	—	—

* Inflection. [1] Determinations by the procedure of Albert, Brown, and Cheeseman (*J.*, 1951, 481). [2] Spectra of all bases, except the diacetyl compound, were determined in 0·1N-NaOH, and those of the cations in 0·1N-HCl. [3] Determined spectroscopically. [4] Spectrum in water at pH 6·10; aged samples of the solid showed no peak at 241 mμ. [5] Unstable in N-HCl.

ciably lowered by the 8-acetyl group, although the pK_a value still exceeded that of pyrimidine. In N-hydrochloric acid, after 4 hours at room temperature, the diacetyl derivative had been hydrolysed to the 5-acetyl compound, as was established by the spectra.

Experimental

The spectrographic work was done on a Unicam S.P. 500 quartz spectrophotometer (kindly lent by the Wool Textile Research Council).

N-Benzyl-2-chloroethylamine.—Thionyl chloride (30 c.c.) was added during 20 min. to a stirred solution of 2-benzylaminoethanol (30 g.) in chloroform (150 c.c.), and the mixture was refluxed for 6 hr. Ether (400 c.c.) was added to the cooled chloroform solution, which was then left in the refrigerator overnight. *N*-Benzyl-2-chloroethylamine hydrochloride was filtered off, and on crystallisation from ethanol (charcoal) gave plates (30·5 g.), m. p. 192°.

4-(N-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl).—(*a*) *N*-Benzyl-2-chloroethylamine hydrochloride (10·3 g.) was gradually added with shaking to a mixture of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (10·4 g.) (Baddiley and Jopham, *J.*, 1944, 678; cf. Albert, Brown, and Wood, *J.*, 1954, 3832) in chloroform (150 c.c.) and sodium hydrogen carbonate (9 g.) in water (30 c.c.), and shaking was continued for a further 20 min. The chloroform layer was separated, washed with water (20 c.c.), and dried (Na_2SO_4), and the chloroform was removed under reduced pressure. The residue, crystallised from methanol, gave *4-(N-benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine* (14·8 g.) as yellow plates, m. p. 95—96° (Found : C, 49·7; H, 4·2. $C_{14}H_{14}O_2N_4Cl_2$ requires C, 49·3; H, 4·1%).

(*b*) A similar preparation with ether (300 c.c.), instead of chloroform, gave 7·5 g. of product, m. p. 95°. Concentration of the methanolic mother-liquor gave *3′-benzyl-2′ : 3′ : 4′ : 5′-tetrahydro-4-methyl-5-nitroglyoxalino-(1′ : 2′-1 : 6)pyrimid-2-one hydrochloride* (2·0 g.) which crystallised from dilute hydrochloric acid as pale yellow prisms, m. p. 230° (decomp.) (Found : C, 52·0; H, 4·5; Cl, 11·4. $C_{14}H_{15}O_3N_4Cl$ requires C, 52·2; H, 4·7; Cl, 11·0%). The hydrochloride, boiled with water or treated with sodium hydrogen carbonate, gave the *base* (IV) which crystallised from water as yellow plates, m. p. 171—172° (Found : C, 58·8; H, 5·0. $C_{14}H_{14}O_3N_4$ requires C, 58·7; H, 4·9%).

This hydrochloride was also prepared from the pyrimidine (I; R = CH_2Ph, X = Cl) (3·0 g.), methanol (80 c.c.), and 2·5N-hydrochloric acid (20 c.c.) at the boil for 45 min. The solution was evaporated to 20 c.c. under reduced pressure, then cooled, and the hydrochloride (2·3 g.) was filtered off.

4-(N-Benzyl-2-hydroxyethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = OH).—2-Benzylaminoethanol (6·0 g.) in ether (30 c.c.) was gradually added with shaking to a mixture of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (8·25 g.) in ether (250 c.c.), and sodium hydrogen carbonate (3·5 g.) in water (10 c.c.). After a further 20 min., evolution of carbon dioxide had ceased, and the ethereal layer was washed with water (20 c.c.), and dried (Na_2SO_4). Removal of the solvent and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave *4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methyl-5-nitropyrimidine* (9·4 g.) as yellow prisms, m. p. 87—88°, raised to m. p. 90° on further crystallisation (Found : C, 51·9; H, 4·4. $C_{14}H_{15}O_3N_4Cl$ requires C, 52·1; H, 4·7%).

5-Amino-4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine.—The above 5-nitropyrimidine (4·0 g.) in ethanol (50 c.c.) was shaken with Raney nickel (5 c.c.; settled suspension) in hydrogen and theoretical uptake was reached after 45 min. The catalyst was filtered off and washed with a little ethanol, and the combined filtrates on concentration gave *5-amino-4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine* (2·9 g.) which crystallised from a small volume of methanol as prisms, m. p. 129—130° (Found : C, 57·6; H, 5·9. $C_{14}H_{17}ON_4Cl$ requires C, 57·4; H, 5·9%).

8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = Cl).—(*a*) 4-(*N*-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (3 g.) in ethanol (100 c.c.) was agitated with Raney nickel (5 c.c.; settled suspension) under hydrogen until the theoretical amount had been absorbed (3 hr.). The catalyst was filtered off and washed with ethanol, and the solvent was removed from the combined filtrates at 60° under reduced pressure. Water was added to the green resin and the solid was filtered off (the filtrate contained nickel as shown by the dimethylglyoxime test). *8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (1·3 g.) crystallised from ethanol as prisms, m. p. 181° (Found : C, 61·4; H, 5·5; Cl, 12·9. $C_{14}H_{15}N_4Cl$ requires C, 61·2; H, 5·5; Cl, 12·9%).

(*b*) 5-Amino-4-(*N*-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine (1·65 g.) was dissolved in phosphoryl chloride (10 c.c.) with gentle warming and the solution kept for 12 hr. Excess of phosphoryl chloride was removed under reduced pressure and the residue, dissolved in water (50 c.c.), was made alkaline with 2N-sodium hydroxide before extraction with chloroform. The solvent was removed from the dried extracts and crystallisation of the residue yielded

8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·2 g.), m. p. 181°, identical with the above.

On treatment with nitrous acid a N-*nitroso*-derivative was obtained, which crystallised from a little methanol in yellow prisms, m. p. 102—103° (Found : C, 55·7; H, 4·7. $C_{14}H_{14}ON_5Cl$ requires C, 55·4; H, 4·6%). The *5-acetyl* derivative was formed by short boiling with acetic anhydride and crystallised from ethanol in prisms, m. p. 151° (Found : C, 60·2; H, 5·1. $C_{16}H_{17}ON_4Cl$ requires C, 60·6; H, 5·4%); the *5-formyl* derivative, prepared by use of formic acid and a little acetic anhydride overnight, crystallised from benzene as needles, m. p. 117° (Found : C, 59·5; H, 5·2. $C_{15}H_{15}ON_4Cl$ requires C, 59·5; H, 5·0%).

8-Benzyl-5 : 6 : 7 : 8-tetrahydro-2-hydroxy-4-methylpteridine (II; R = CH_2Ph, X = OH).—(*a*) 8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (0·5 g.) and constant-boiling hydrobromic acid (10 c.c.) were refluxed for 1½ hr. and the excess of acid was removed under reduced pressure. The residue was dissolved in water (25 c.c.) and extracted with chloroform to remove some benzyl bromide. The aqueous solution was then neutralised with sodium hydrogen carbonate and extracted with chloroform. The residue from the extracts was crystallised from ethanol and gave *8-benzyl-5 : 6 : 7 : 8-tetrahydro-2-hydroxy-4-methylpteridine* (0·18 g.) as plates, m. p. 260° (decomp.) (Found : C, 65·5; H, 6·3. $C_{14}H_{16}ON_4$ requires C, 65·6; H, 6·3%).

(*b*) In a similar reaction, but with 5N-hydrochloric acid (10 c.c.) replacing hydrobromic acid, the 2-chloro-compound (2·25 g.) gave the above 2-hydroxypteridine (0·95 g.), and no benzyl chloride was detected.

The reduction of (II; R = CH_2Ph, X = OH) by sodium in liquid ammonia produced unstable products which rapidly decomposed in solution.

8-Benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = H).—(*a*) 8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (2·0 g.) in ethanol (100 c.c.) was shaken with 2% palladium–calcium carbonate (0·5 g.) under hydrogen. After filtration and removal of the solvent, the residue was dissolved in water (50 c.c.) and extracted with ether to remove a small amount of starting material. The aqueous layer was treated with sodium hydrogen carbonate and extracted with ether. Removal of the ether, followed by crystallisation of the residue from light petroleum (b. p. 60—80°), gave *8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (1·3 g.) as prismatic needles, m. p. 93—94° (Found : C, 70·0; H, 6·6. $C_{14}H_{16}N_4$ requires C, 69·9; H, 6·7%).

(*b*) A similar reduction of the 2-chloro-compound (1·0 g.) in acetic acid (100 c.c.) was done with 5% palladised charcoal (0·5 g.) at an initial pressure of 4 atm. of hydrogen. Treatment as in (*a*) gave the product (0·75 g.), m. p. 93—94°, as above.

(*c*) Finely ground 2-chloro-compound (2·0 g.) was added gradually to anhydrous liquid ammonia (150 c.c.) followed by sodium (about 0·3 g.; in pieces) until the reaction slowed, as judged by the rate of disappearance of the blue colour. Ammonium chloride was then added to change the solution from orange to grey and the ammonia was allowed to evaporate completely, the flask being fitted with a potassium hydroxide tube. The residue was extracted with ether (3 × 50 c.c.) and the extracts, after being washed with water (20 c.c.) to remove any debenzylated material, gave 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·2 g.), m. p. 93—94°.

The *5-acetyl* derivative crystallised from light petroleum (b. p. 100—120°) in plates, m. p. 121—122° (Found : C, 67·6; H, 6·5. $C_{16}H_{18}ON_4$ requires C, 68·1; H, 6·4%) : the *5-formyl* derivative was prepared by means of formic acid and acetic anhydride at room temperature overnight, and crystallised from light petroleum (b. p. 100—120°) as prisms, m. p. 102° (Found : C, 66·7; H, 6·4. $C_{15}H_{16}ON_4$ requires C, 67·2; H, 6·0%).

5 : 6 : 7 : 8-*Tetrahydro-4-methylpteridine* (II; R = X = H).—(*a*) Sodium (0·7 g., 4 atomic equivs.) was added to 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (2·0 g.) in liquid ammonia (100 c.c.) and, after 2 hr., ammonium chloride was added. The product was worked up as above (but without the water-washing) and gave *5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·82 g.) as needles [from benzene (charcoal)], m. p. 145—146° (Found : C, 56·0; H, 6·8. $C_7H_{10}N_4$ requires C, 56·0; H, 6·7%).

The *picrate* crystallised from ethanol as deep orange prisms, m. p. 263° (Found : C, 41·1; H, 3·6. $C_7H_{10}N_4,C_6H_3O_7N_3$ requires C, 41·2; H, 3·5%), and the *methiodide* from propanol as deep cream needles, m. p. 272—274° (Found : C, 33·0; H, 4·3. $C_7H_{10}N_4,CH_3I$ requires C, 32·9; H, 4·5%). Boiling acetic acid gave the *acetate* which crystallised from benzene as prisms, m. p. 114° (Found : C, 51·9; H, 6·7. $C_7H_{10}N_4,C_2H_4O_2$ requires C, 51·4; H, 6·7%).

The tetrahydropteridine (0·2 g.) was formylated by treatment for 24 hr. with formic acid (10 c.c.) and acetic anhydride (2 c.c.) at room temperature. Excess of reagents was removed under reduced pressure and the residue was refluxed in ethanol (10 c.c.) for 10 min. After

removal of the ethanol, the *5-formyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·15 g.) crystallised from benzene (charcoal) as needles, m. p. 194° (Found: C, 54·5; H, 5·7; N, 32·0. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·7; N, 31·5%). Formylation of the tetrahydropteridine with formic acetic anhydride at room temperature overnight gave the *5 : 8-diformyl* derivative, which crystallised from benzene as prisms, m. p. 170—171° (Found: C, 52·1; H, 4·6. $C_9H_{10}O_2N_4$ requires C, 52·4; H, 4·9%).

Boiling acetic anhydride (10 c.c.) and the tetrahydropteridine (0·5 g.) gave in 10 min. *5 : 8-diacetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·4 g.) which crystallised from benzene (charcoal) as prisms, m. p. 168° (Found: C, 56·9; H, 6·0; N, 23·8. $C_{11}H_{14}O_2N_4$ requires C, 56·4; H, 6·0; N, 23·9%).

(*b*) 8-Benzyl-2-chloro-5-formyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·6 g.) was added to anhydrous liquid ammonia, followed by sodium (0·75 g., 6 atomic equivs.). After 10 min., the excess of sodium was removed by ammonium chloride, and the ammonia was allowed to evaporate. Extraction of the residue with chloroform, followed by chromatography of the extracts on alumina with the same solvent, yielded the 8-benzyltetrahydro-4-methylpteridine (0·05 g.), m. p. 93°, and then 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (0·32 g.), m. p. 142°. No product containing a formyl group was isolated.

5-Acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine.—5-Acetyl-8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (3·2 g.) was dissolved in liquid ammonia (150 c.c.) and reduced with sodium (0·93 g.). After 20 min., excess of ammonium chloride was added and the ammonia was allowed to evaporate. The residue was extracted with chloroform, chromatographed on an alumina column, and yielded *5-acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·5 g.) which crystallised from butanone as prisms, m. p. 182° (Found: C, 56·4; H, 6·2. $C_9H_{12}ON_4$ requires C, 56·2; H, 6·3%).

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Configurational Studies in Synthetic Analgesics.

By A. H. BECKETT and A. F. CASY.

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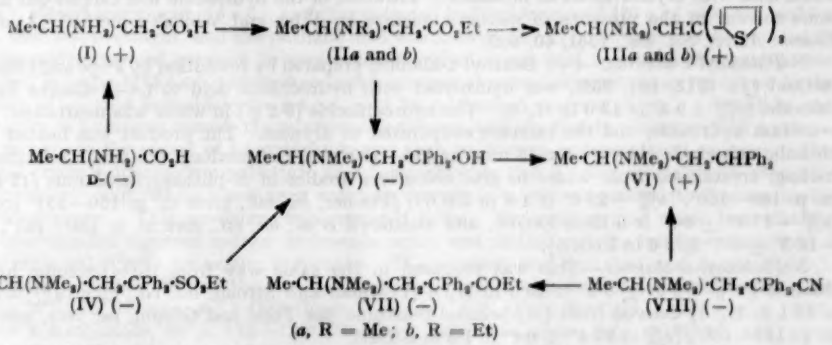
The analgesically active isomers "(−)-Methadone" [(−)-6-dimethylamino-4 : 4-diphenylheptan-3-one] (VII), (−)-3-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV), "(+)-Dimethylthiambutene" [(+)-3-dimethylamino-1 : 1-di-2′-thienylbut-1-ene] (III*a*), and "(+)-Diethylthiambutene" [(+)-3-diethylamino-1 : 1-di-2′-thienylbut-1-ene] (III*b*), have been shown to possess identical configurations which are related to D-(−)-alanine.

IT has been shown that, in synthetic analgesics possessing one asymmetric carbon atom, nearly all the analgesic activity exhibited by the racemic mixture resides in one of the isomers. In an investigation of the structural requirements of analgesics it was of importance, therefore, to determine the configuration of certain of these highly active enantiomorphs. The configurations have been determined by reactions outlined in the annexed scheme.

β-Aminobutyric acid (I) was obtained from alanine by application of an Arndt–Eistert reaction according to a modification of the method of Balenović, Cerar, and Fuks (*J.*, 1952, 3316), preliminary work being done on racemic material. The Wolff rearrangement, involving migration of an asymmetric group, has been shown to proceed with retention of configuration (Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 500). *N*-Phthaloylalanine was converted *via* its acid chloride into 1-diazo-3-phthalimidobutan-2-one and the diazo-ketone rearranged to methyl β-phthalimidobutyrate : silver benzoate (see Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163) proved to be more efficient as catalyst than the silver oxide used by the original workers. Treatment of the diazo-ketone with alcoholic ammonia and silver nitrate gave

β-phthalimidobutyramide. The structures of the two products of rearrangement were confirmed by their direct synthesis from β-aminobutyric acid prepared by hydrolysis of ethyl β-aminobutyrate. This ester was obtained by condensing ethyl crotonate with ammonia according to Adamson's method (*J.*, 1950, 885). The β-phthalimidobutyric acid derivatives were hydrolysed to β-aminobutyric acid hydrochloride by a mixture of concentrated hydrochloric acid and glacial acetic acid. The use of 50% hydriodic acid for the hydrolysis (Balenović *et al.*, *loc. cit.*) gave a product which could not be methylated by reductive methylation, probably owing to poisoning of the catalyst by iodine.



The (+) and (−) denote sterically related compounds of the series, and not necessarily those isomers with which the reactions were carried out.

Optically active *N*-phthaloyl-L-alanine, $[\alpha]_D^{18}$ −23·6° (*idem*, *loc. cit.*, report −17·5°), was prepared by heating a mixture of neutralised L-alanine hydrochloride and phthalic anhydride for 15 min. at 170—180° (cf. Bilman, *J. Amer. Chem. Soc.*, 1948, **70**, 1473). The lower value of the specific rotation given by Balenović *et al.* (*loc. cit.*) agrees with the value originally reported by Fischer (*Ber.*, 1907, **40**, 489) for material prepared by heating a mixture of alanine and phthalic anhydride for 7 hr. at 120—125°, a process which was shown to give a partially racemised product. The optical purity of the intermediates used along the route to 3-dimethylamino-1 : 1-diphenylbutan-1-ol (V) is indicated by the numerical identity of the specific rotations of this final product and material obtained by the resolution of the corresponding racemic mixture.

Reductive methylation of β-aminobutyric acid hydrochloride, derived from D-(−)alanine, by the method applied by Bowman and Stroud (*J.*, 1950, 1342) to α-amino-acids, followed by esterification of the product, gave ethyl β-dimethylaminobutyrate (II*a*). This ester with phenylmagnesium bromide gave the (−)-amino-alcohol (V), the hydrolysis product of (−)-3-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV) (Archer and Auerbach, *J. Amer. Chem. Soc.*, 1951, **73**, 1840). The (+)-amino-alcohol (V), obtained by resolution of the racemic compound with (+)-tartaric acid, was dehydrated by Archer and Auerbach's method (*loc. cit.*) to (−)-3-dimethylamino-1 : 1-diphenylbut-1-ene which, on hydrogenation, gave (−)-3-dimethylamino-1 : 1-diphenylbutane (VI). (−)-3-Dimethylamino-1 : 1-diphenylbutyl cyanide (VIII), the precursor of " (−)-Methadone " (VII) gave, on cleavage with sodamide, the (+)-aminobutane (VI) which, from the foregoing work, must be related to the (−)-amino-alcohol (V). Thus the analgesically active isomers " (−)-Methadone " (VII) and the (−)-sulphone (IV) are both related to D-(−)-alanine. Ethyl β-dimethylaminobutyrate, derived from L-(+)-alanine, upon reaction with thienyl-lithium, gave (−)-3-dimethylamino-1 : 1-di-2′-thienylbutan-1-ol which was dehydrated by dry hydrogen chloride to yield (−)-3-dimethylamino-1 : 1-di-2′-thienylbut-1-ene (III*a*), the analgesically active (+)-isomer therefore being related to D-(−)-alanine. Reductive ethylation of β-aminobutyric acid hydrochloride, derived from D-(−)alanine, was carried out by Bowman's method (*J.*, 1950, 1346), and esterification of the product gave ethyl β-diethylaminobutyrate (II*b*). This ester, on reaction with thienyl-lithium followed by dehydration of

the resulting 3-diethylamino-1 : 1-di-2′-thienylbutan-1-ol, gave analgesically active (+)-3-diethylamino-1 : 1-di-2′-thienylbut-1-ene (III*b*) which is thus related to D-(−)-alanine.

The significance of these configurational relations in connection with the stereochemical requirements of analgesics has been discussed elsewhere (Beckett and Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986).

Experimental

Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equiv. wts. of the bases were determined by titration with 0·02N-perchloric acid in glacial acetic acid with crystal-violet as indicator. Titration of the hydriodide was carried out in the same solvent in the presence of mercuric acetate by Pifer and Wollish's method (*J. Amer. Pharm. Assoc., Sci. Ed.*, 1951, **40**, 609).

N-Phthaloyl-L-alanine.—(+)-Benzoyl-L-alanine, prepared by resolution by Pope and Gibson's method (*J.*, 1912, **101**, 939), was hydrolysed with hydrochloric acid to L-(+)-alanine hydrochloride, $[\alpha]_D^{21}$ +9·5° (*c* 13·0 in H_2O). The hydrochloride (9·2 g.) in water was neutralised with N-sodium hydroxide, and the mixture evaporated to dryness. The product was heated with phthalic anhydride (11·9 g.) for 15 min. at 170—180° and the resultant oil, which solidified on cooling, crystallised from water to give colourless needles of *N*-phthaloyl-L-alanine (13·4 g.), m. p. 149—150°, $[\alpha]_D^{20}$ −23·6° (*c* 1·8 in EtOH) {Fischer, *loc. cit.*, gives m. p. 150—151° (corr.), $[\alpha]_D^{20}$ −17·8° ± 0·2° (*c* 8·13 in EtOH), and Balenović *et al.*, *loc. cit.*, give m. p. 150—151°, $[\alpha]_D^{20}$ −18·3° ± 0·7° (*c* 2·6 in EtOH)}.

N-Phthaloyl-D-alanine.—This was prepared in the same way from D-(−)-alanine hydrochloride ($[\alpha]_D^{21}$ −9·9° ± 0·2° (*c* 13·0 in H_2O) {Bowman and Stroud, *loc. cit.*, give $[\alpha]_D^{18}$ −9·13° (*c* 13·1 in H_2O)} derived from (−)-benzoyl-D-alanine (see Pope and Gibson, *loc. cit.*), and had m. p. 149—150°, $[\alpha]_D^{20}$ +23·4° ± 0·5° (*c* 1·8 in EtOH).

1-*Diazo*-3-*phthalimidobutan*-2-*one.*—*N*-Phthaloylalanine (10 g.) and redistilled thionyl chloride (10 c.c.) were heated for 1 hr. at 60° and the excess of thionyl chloride removed under reduced pressure. The crude *N*-phthaloylalanyl chloride (10·5 g.), after being kept overnight in a vacuum-desiccator, was dissolved in benzene (50 c.c.) and added dropwise to a stirred, ice-cooled solution of diazomethane in ether (250 c.c.; prepared from methyl *N*-nitroso-2-methylamino*iso*butyl ketone, 30 g.). The mixture was stirred for 1 hr. at room temperature, then left for 2 hr., and the solvent and excess of diazomethane were removed by distillation. The residue crystallised from ethyl acetate–light petroleum (b. p. 40—60°) to give the diazo-ketone (9 g.), m. p. 107—108° (Balenović, *Experientia*, 1947, **3**, 369, gives m. p. 111°).

The (−)-isomer, prepared in the same way from (−)-*N*-phthaloyl-L-alanine, was obtained as an orange-coloured oil, $[\alpha]_D^{24}$ −88·5° ± 1° (*c* 0·5 in ethyl acetate) {Balenović *et al.*, *loc. cit.*, give m. p. 88°, $[\alpha]_D^{18}$ −69·3° ± 1° (*c* 0·48 in ethyl acetate)}.

The (+)-isomer, prepared from (+)-*N*-phthaloyl-D-alanine, was obtained as an orange-coloured oil, $[\alpha]_D^{17}$ +86·7° ± 0·3°.

Rearrangement of 1-*Diazo*-3-*phthalimidobutan*-2-*ones.*—(a) *Methyl* β-*phthalimidobutyrate.* A 7% solution (4 c.c.) of silver benzoate in triethylamine was added dropwise during 2 hr. to a stirred solution of the diazo-ketone (2 g.) in methanol (50 c.c.). The mixture was refluxed for a few minutes with charcoal, filtered, and evaporated to dryness, to give a pale yellow oil which rapidly solidified. The solid was extracted several times with hot light petroleum (b. p. 40—60°), the combined extracts were evaporated to dryness, and the residual solid (1·9 g.) crystallised from ethanol to give colourless plates of *methyl* β-*phthalimidobutyrate*, m. p. 61° (Found: C, 63·6; H, 5·3; N, 5·8. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

The (−)-isomer, prepared in the same way from the (+)-diazo-ketone, was obtained as a yellow liquid, b. p. 140—144°/0·7 mm., $[\alpha]_D^{23}$ −33·1° ± 0·5° (*c* 0·5 in C_6H_6) {*idem*, *loc. cit.*, give m. p. 38°, $[\alpha]_D^{14}$ +26·3° ± 1° (*c* 0·26 in C_6H_6) for the (+)-isomer}.

(b) β-*Phthalimidobutyramide.* A mixture of the diazo-ketone (1 g.), methanol saturated with ammonia (20 c.c.), and a saturated solution of silver nitrate in 80% (aqueous) methanol (2·5 c.c.) was gently warmed. When evolution of gas ceased, the mixture was refluxed for 30 min. and the solvent and excess of ammonia were removed under reduced pressure. The residue was refluxed with a slight excess of alcoholic hydrochloric acid (and charcoal), and the mixture filtered and concentrated to give, on cooling, feathery crystals of β-*phthalimidobutyramide* (0·4 g.), m. p. 188—189° (Found: C, 61·7; H, 4·85; N, 12·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

The (+)-isomer prepared in the same way from the (−)-diazo-ketone had m. p. 200°, $[\alpha]_D^{19}$ +46·1° (*c* 0·5 in EtOH).

β-Phthalimidobutyric Acid and its Derivatives.—β-Aminobutyric acid (2 g.), m. p. 190—191° (Fischer and Grah, *Annalen*, 1911, **383**, 365, give m. p. 188—189°), prepared by hydrolysis of ethyl β-aminobutyrate, was heated with phthalic anhydride (3·45 g.) for 15 min. at 180—185°. The product solidified on cooling and crystallised from water, to give colourless needles of *β-phthalimidobutyric acid* (3·5 g.), m. p. 122—123° (Found: C, 60·1; H, 4·7; N, 5·9. $C_{12}H_{11}O_4N,\frac{1}{2}H_2O$ requires C, 59·5; H, 5·0; N, 5·8%). The methyl ester, prepared by using diazomethane, had m. p. 61°, alone or mixed with a specimen derived from the diazo-ketone. The amide, prepared by the action of ammonia on the acid chloride, had m. p. 188°, alone or mixed with a specimen derived from the diazo-ketone.

3-Dimethylamino-1 : 1-diphenylbutan-1-ol (V).—A mixture of methyl β-phthalimidobutyrate (6·5 g.), glacial acetic acid (16 c.c.), and concentrated hydrochloric acid (20 c.c.) was refluxed for 7 hr., then left overnight, and the phthalic acid was filtered off. The filtrate was evaporated to dryness under reduced pressure to give crude β-aminobutyric acid hydrochloride, which was dissolved in water (115 c.c.), and shaken with hydrogen at room temperature and pressure in the presence of aqueous formaldehyde (8·4 c.c.) and 5% palladised charcoal (6 g.). After 48 hr. the absorption of hydrogen ceased, the mixture was filtered, and the filtrate evaporated on a steam-bath to remove the excess of formaldehyde and then to dryness under reduced pressure. The residual crude β-dimethylaminobutyric acid hydrochloride (3·5 g.) was treated with ethanolic N-hydrochloric acid (60 c.c.) and next morning the mixture was evaporated to dryness under reduced pressure. This procedure was repeated twice. The residue was made just alkaline with concentrated aqueous sodium hydroxide, ether was added, and the mixture made into a slurry with anhydrous potassium carbonate. The solution was decanted and dried (K_2CO_3), the ether evaporated off, and the residue distilled to give ethyl β-dimethylaminobutyrate (IIa) (2·1 g.), b. p. 66°/16 mm., n_D^{19} 1·4260 (Found: equiv., 159. Calc. for $C_8H_{17}O_2N$: equiv., 159). It gave a methiodide, m. p. 129—130° (Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412, gives m. p. 127—128°). The ester (1·5 g.) was treated with phenylmagnesium bromide according to Kjaer and Petersen's method (*Acta Chem. Scand.*, 1951, **5**, 1145), to give colourless plates of 3-dimethylamino-1 : 1-diphenylbutan-1-ol (V) (1 g.), m. p. 121—122° (*idem, loc. cit.*, give m. p. 123°).

The (−)-isomer, prepared in the same way using ethyl β-dimethylaminobutyrate derived from (−)-methyl β-phthalimidobutyrate, had m. p. 148—149°, $[\alpha]_D^{17}$ −46·8° ± 0·8° (*c* 1·0 in 0·08N-HCl) {Archer and Auerbach, *loc. cit.*, give m. p. 150·6—152·2° (corr.), $[\alpha]_D^{24}$ −41·1° (*c* 2·3 in aq. HCl) for material obtained by hydrolysis of (−)-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV)}.

Resolution of 3-Dimethylamino-1 : 1-diphenylbutan-1-ol (V).—The amino-alcohol (2·7 g.) and (+)-tartaric acid (1·5 g.) were dissolved in a hot mixture of acetone (17·5 c.c.) and 96% ethanol (17·5 c.c.). The crystals which were formed on cooling were recrystallised twice from the same solvent, to give the (+)-amino-alcohol (+)-tartrate (0·65 g.), m. p. 186—188°, $[\alpha]_D^{24}$ +40·0° ± 0·5° (*c* 0·9 in H_2O). The base was liberated with dilute aqueous ammonia and crystallised from ethanol to give the (+)-amino-alcohol, m. p. 149—150°, $[\alpha]_D^{24}$ +47·0° (*c* 0·8 in 0·08N-HCl).

(−)-*3-Dimethylamino-1 : 1-diphenylbut-1-ene.*—This, prepared from the (+)-amino-alcohol by Archer and Auerbach's method (*loc. cit.*), had $[\alpha]_D^{19}$ −170° (*c* 1·0 in EtOH), and gave a picrate, yellow needles (from ethanol), m. p. 165—167° {*idem, loc. cit.*, give $[\alpha]_D^{20}$ +149° (*c* 1·0 in EtOH) for the (+)-isomer and m. p. 164·5° for its picrate}.

(−)-*3-Dimethylamino-1 : 1-diphenylbutane* (VI).—The (−)-amino-butene hydrochloride (0·4 g.) in ethanol (10 c.c.) and 5% palladised charcoal (0·5 g.) were shaken with hydrogen at room temperature and pressure. After 4 hr., when absorption had ceased, the mixture was filtered and evaporated to dryness, and the base, which was liberated with dilute aqueous ammonia, was extracted with ether. After drying (Na_2SO_4) the ether was removed to give the (−)-amino-butane (0·35 g.) as a pale yellow oil which formed a hydrochloride, colourless needles (from ether–ethanol), m. p. 180—182°, $[\alpha]_D^{20}$ −42·7° (*c* 0·8 in H_2O) {Eddy, May, and Mosettig, *J. Org. Chem.*, 1952, **17**, 321, give m. p. 180—182°, $[\alpha]_D^{20}$ −43·3° (*c* 1·04 in H_2O) for material derived from "(+)-Methadone"}, and a picrate, yellow plates (from ethanol), m. p. 132° [see below for the picrate of the corresponding (+)-amino-butane].

Cleavage of (−)-3-Dimethylamino-1 : 1-diphenylbutyl Cyanide (VIII).—The (−)-amino-cyanide was cleaved by the method of Klenk, Suter, and Archer (*J. Amer. Chem. Soc.*, 1948, **70**, 3846) to give (+)-3-dimethylamino-1 : 1-diphenylbutane (VI) as a pale yellow oil. The latter gave a hydrochloride, m. p. 183—184°, from acetone, $[\alpha]_D^{19}$ +52·7° (*c* 1·0 in H_2O) {Eddy *et al.*, *loc. cit.*, give m. p. 179—181°, [α] +43·1° (*c* 0·53 in H_2O)}, and a *picrate*, yellow plates (from

ethanol), m. p. 132° (Found : C, 59·65; H, 5·4; N, 11·5. $C_{24}H_{26}O_7N_4$ requires C, 59·75; H, 5·4; N, 11·6%).

(−)-3-*Dimethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene Hydrobromide*.—(−)-3-*Dimethylamino*-1 : 1-*di*-2′-*thienylbutan*-1-*ol* was prepared from ethyl β-dimethylaminobutyrate (II*a*) [derived from (+)-β-phthalimidobutyramide] by reaction with thienyl-lithium according to Adamson's method (*loc. cit.*). It had m. p. 96—97°, $[\alpha]_D^{18}$ −56·5° ± 0·3° (*c* 0·9 in EtOH) (Found : C, 59·6; H, 6·5; N, 5·1; S, 22·9. $C_{14}H_{19}ONS_2$ requires C, 59·8; H, 6·8; N, 5·0; S, 22·8%). Dry hydrogen chloride was passed for 10 min. through a solution of the amino-alcohol (0·23 g.) in chloroform (2 c.c.), the solvent removed under reduced pressure, and the residue in water stirred with charcoal for a few minutes at 60°. The mixture was filtered, and the base liberated with dilute aqueous ammonia, and extracted with ether. After drying (Na_2SO_4), the solvent was removed to give the (−)-amino-butene (III*a*) (0·18 g.) as a yellow oil. It gave a *hydrobromide*, pale buff plates (from ether–ethanol), m. p. 163—164°, $[\alpha]_D^{22}$ −104° ± 1° (*c* 0·4 in H_2O) (Found : C, 49·1; H, 5·2; N, 3·95; S, 18·4. $C_{14}H_{18}NS_2Br$ requires C, 48·8; H, 5·2; N, 4·1; S, 18·6%).

3-*Diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene Hydriodide*.—β-Aminobutyric acid (I) (2 g.), in water (80 c.c.), was shaken with hydrogen at room temperature and pressure in the presence of acetaldehyde (3·5 g.) and 5% palladised charcoal (4 g.). After 24 hr. the absorption of hydrogen ceased, and the mixture was filtered and evaporated to dryness under reduced pressure. The residual crude β-diethylaminobutyric acid (2·8 g.) was esterified by the method described above for β-dimethylaminobutyric acid, to give ethyl β-diethylaminobutyrate (II*b*) (2·2 g.), b. p. 98—100°/20 mm., n_D^{19} 1·4292 (Found : equiv., 188. Calc. for $C_{10}H_{21}O_2N$: equiv., 187). It gave a *styphnate*, yellow needles (from ethanol), m. p. 67·5—68·5° (Found : C, 44·65; H, 5·55; N, 13·1. $C_{16}H_{24}O_{10}N_4$ requires C, 44·4; H, 5·6; N, 13·0%). The amino-ester, on reaction with thienyl-lithium, gave 3-diethylamino-1 : 1-di-2′-thienylbutan-1-ol, m. p. 74—75° (*idem*, *loc. cit.*, gives m. p. 75—76°). The amino-alcohol was converted into the amino-butene (III*b*) by the method described above for the corresponding dimethylamino-compound. It gave a *hydriodide*, colourless plates (from ether–ethanol), m. p. 147—148° (Found : C, 46·3; H, 5·1. $C_{16}H_{22}NS_2I$ requires C, 45·8; H, 5·25%).

The (+)-*hydriodide*, prepared in the same way by using ethyl β-diethylaminobutyrate derived from (−)-methyl β-phthalimidobutyrate, had m. p. 139—140°, $[\alpha]_D^{20}$ +109° ± 2° (*c* 0·9 in EtOH) (Found : C, 45·4; H, 5·0; N, 3·2; S, 15·5%; equiv., 417. $C_{16}H_{22}NS_2I$ requires C, 45·8; H, 5·25; N, 3·3; S, 15·3%; equiv., 419).

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The Structure of Hydrojuglone Glucoside.

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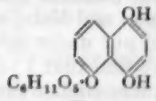
[Reprint Order No. 5899.]

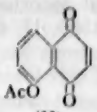
When 5-acetoxy-1 : 4-naphthaquinol (III) reacts with diazomethane the acetyl group is displaced and migrates to the *peri*-position, giving 4-acetoxy-1 : 5-dimethoxynaphthalene (VI; R = Ac). From this and the earlier work of Ruelius and Gauhe and of Daglish it follows that the naturally occurring α-hydrojuglone glucoside is the 4- (VIII) and not the 5-glucoside (I) of 1 : 4 : 5-trihydroxynaphthalene.

It has been found by Daglish (*Biochem. J.*, 1950, **47**, 452) and by Ruelius and Gauhe (*Annalen*, 1951, **571**, 69) that juglone occurs in walnut tissues (*Juglans regia*) as a glucoside of α-hydrojuglone (1 : 4 : 5-trihydroxynaphthalene). They all considered the glucose moiety to be attached at position 5 (cf. I). Ruelius and Gauhe showed that methylation of the glucoside with diazomethane, followed by removal of the glucose residue, gave a dimethoxynaphthol, m. p. 155—156°, identical with that obtained from juglone acetate (II) by catalytic reduction, methylation (with diazomethane), and final hydrolysis. This was regarded as (IV), and the glucoside consequently as (I). However, 5 : 8-dimethoxy-1-naphthol has been obtained by Asano and Hase (*J. Pharm. Soc. Japan*, 1943, **63**, 83;

Chem. Abs., 1952, **46**, 92) by a standard procedure: quinol dimethyl ether was condensed with succinic anhydride in the presence of aluminium chloride, the resulting keto-acid was reduced and cyclised to 5 : 8-dimethoxy-1-tetralone (Thomson, *J.*, 1952, 1822), and the latter dehydrogenated to give a naphthol, m. p. 103—104°. This is authentic (IV).

After various attempts to convert the naphthol of Ruelius and Gauhe into 5 : 8-dimethoxy-1 : 4-naphthaquinone by standard methods had failed, the compound was oxidised with chromium trioxide in acetic acid. This yielded juglone methyl ether (V)


(I)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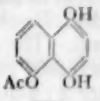
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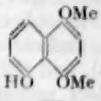
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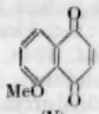
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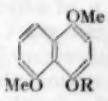
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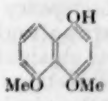
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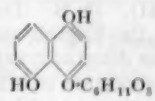
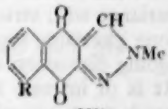

(VIII)


(IX)

together with an unidentified product of high m. p. This indicated that Ruelius and Gauhe's dimethoxynaphthol was in fact (VI; R = H) or (VII); the former structure was confirmed by another synthesis starting from juglone methyl ether. Catalytic reduction of the ether (V) followed by methylation with diazomethane gave the dimethyl ether (VI; R = H) identical with the dimethoxynaphthol obtained from (II). The alternative structure (VII) is ruled out by the fact that 1 : 8-dihydroxynaphthalene forms only a monomethyl ether with diazomethane (Boeseken and Smith, *Rec. Trav. chim.*, 1939, **58**, 125) and by the low solubility of the naphthol in aqueous sodium hydroxide. Since, in the original synthesis, the reduction product (III) can be re-oxidised to the starting material (II), an unusual reaction must take place at the methylation stage. It is known that *O*-acetyl groups can be displaced by reaction with diazomethane in the presence of water to give methyl ethers (Herzig and Tichatschek, *Ber.*, 1906, **39**, 268, 1557) and evidently in this case the neighbouring hydroxyl group functions in the same way, the displaced acetyl group in (III) migrating to the *peri*-position to yield the ether (VI; R = Ac). The mechanism is obscure. Similar migrations of acyl groups during reactions with diazomethane have been observed in compounds containing two *o*-hydroxyl groups: *e.g.*, alizarin 2-acetate reacts with diazomethane to form 1-acetoxy-2-methoxyanthraquinone (Kubota and Perkin, *J.*, 1925, **127**, 1889), and other examples were found amongst derivatives of anthragallol and gallacetophenone (Perkin and Storey, *J.*, 1928, 229; 1929, 1399). In all these cases the hydroxyl groups were close to a carbonyl group which was thought to have an important influence on the reaction. The explanation put forward at that time is inadequate but the postulated cyclic intermediate seems reasonable as the migration occurs only when the hydroxyl groups are in the *ortho*- (in the present case *peri*-) position. The migration of acyl groups in mono- and di-glycerides is also considered to proceed *via* cyclic intermediates.

The natural product must therefore be (VIII) unless a similar migration of the glucose residue occurs during the reaction of the glucoside with diazomethane. This is very unlikely. There are many examples of the treatment of glycosides with diazomethane [*e.g.*, Hasagawa, *Acta phytochim.* (*Tokyo*), 1940, **11**, 299; Zemplen and Bognár, *Ber.*, 1941, **74**, 1785; Kuhn and Löw, *Ber.*, 1944, **77**, 196] but no anomalies have been reported, and we found that phenyl and 2-naphthyl tetra-*O*-acetyl-β-D-glucoside were unaffected when treated with excess of moist ethereal diazomethane. The natural product has been synthesised by Daglish (*J. Pharm. Pharmacol.*, 1952, **4**, 539) from both α- and β-hydrojuglone and, in very low yield, from juglone but none of these syntheses establishes the structure. Under the conditions used β-hydrojuglone would rapidly enolise and, in the case of juglone, reduction evidently occurred at some stage, probably before glucoside formation. We have failed to prepare juglone glucoside, which is not surprising as even

methylation has never been achieved. In support of structure (I) Daglish (*loc. cit.*, 1950) drew attention to the reducing properties of the glucoside and the similarity of its ultraviolet absorption curve to that of the acetate (III). As naphthols in general show reducing properties (and Daglish's material was not pure) simple tests with ammoniacal silver nitrate, etc., are not very significant, and as the light absorption is broadly similar to that of 1 : 5-dihydroxy- and 1 : 4 : 5-trihydroxy-naphthalene (Daglish, *J. Amer. Chem. Soc.*, 1950, **72**, 4859) it does not exclude structure (VIII). The occurrence of this glucoside in walnut tissues interferes with the determination of ascorbic acid by titration with 2 : 6-dichlorophenol-indophenol (Daglish, *Biochem. J.*, 1950, **47**, 462; Wokes and Melville, *ibid.*, 1949, **45**, 343, and earlier papers). The dye titrations were carried out under acid conditions (pH <4), and the titre increased as the pH was lowered. We find that 1 : 5-dihydroxynaphthalene will also reduce 2 : 6-dichlorophenol-indophenol under similar conditions, the reduction being very rapid at low pH. The dye titrations are therefore not at variance with structure (VIII). [N.B. The large discrepancy in the m. p. of α-hydrojuglone glucoside reported by the English and the German workers does not affect the foregoing discussion as the same dimethoxynaphthol was obtained in each laboratory.]

It is of interest that the abnormal reaction of the acetate (III) with diazomethane proceeds more smoothly than is the case with 1 : 4-naphthaquinols in general. Smith and Webster (*J. Amer. Chem. Soc.*, 1937, **59**, 666) were unable to obtain 1 : 4-dimethoxy-2-methylnaphthalene from 2-methylnaphthaquinol, and Moore and Waters (*J.*, 1953, 3405) obtained the diazole (IX; R = H) by reaction of diazomethane with 1 : 4-naphthaquinol. We found that treatment of α-hydrojuglone with excess of diazomethane gave a dark oil from which a diazole (IX; R = OMe) was isolated in low yield. No other product could be identified. Perkin and Storey (*loc. cit.*) noted that methylations with diazomethane were occasionally accompanied by oxidation.

Experimental

4 : 8-*Dimethoxy*-1-*naphthol*.—(*a*) Ruelius and Gauhe's procedure (*loc. cit.*) was modified as follows: Juglone acetate (2·16 g.) in chloroform (30 c.c.) and methanol (30 c.c.) was hydrogenated over Adams catalyst (0·2 g.). When hydrogen uptake was complete, the solution was cooled in ice and then decanted into dry ice-cold ethereal diazomethane (from 10 g. of nitrosomethylurea). Next day the solution was evaporated to dryness *in vacuo*. The residual pale orange solid (a portion crystallised from aqueous alcohol had m. p. 117°) was dissolved in warm ethanol (20 c.c.), heated on a steam-bath for 5 min. with aqueous sodium hydroxide (10 c.c.; 2N), and then poured on ice and hydrochloric acid. The crude naphthol was collected, washed, dried, sublimed at 120—130°/0·05 mm., and crystallised from ethanol in leaflets, m. p. 155—156° (46%). (When a portion of the naphthaquinol solution was shaken with silver oxide juglone acetate was regenerated.)

(*b*) Juglone methyl ether (0·4 g.) in chloroform (30 c.c.) and methanol (30 c.c.) was hydrogenated as above and the resulting naphthaquinol solution (a portion shaken with silver oxide yielded starting material) decanted into excess of diazomethane in dry ether. Removal of the solvents next day left crude naphthol which was sublimed at 120°/0·05 mm. and crystallised from ethanol in leaflets, m. p. 155—156° (30%), identical with those obtained as in (*a*) above. The acetate had m. p. and mixed m. p. 119°.

(*c*) The same naphthol was obtained by reaction of 1 : 4 : 5-trihydroxynaphthalene in aqueous potassium hydroxide under nitrogen with a large excess of methyl sulphate. Ether-extraction of the alkaline solution yielded a crude solid from which 4 : 8-dimethoxy-1-naphthol was obtained by sublimation.

Oxidation.—A solution of chromium trioxide (0·5 g.) in water (2 c.c.) was added to a suspension of the naphthol (0·5 g.) in glacial acetic acid (10 c.c.) and the mixture gently warmed for 2—3 min. until dissolution was complete and yellow crystals began to separate. These were collected after 3 hr. and the filtrate was diluted with water and extracted with chloroform. The extract was shaken with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving a residue which crystallised from alcohol in fine orange-brown needles, m. p. 186° (170 mg.), undepressed on admixture with juglone methyl ether. The yellow crystals, m. p. *ca.* 270° (55 mg.), were insoluble in aqueous alkali but dissolved in warm alcoholic sodium hydroxide.

5'-Methoxy-1-methylnaphthaquinono(3' : 2'-3 : 4)pyrazole.—1 : 4 : 5-Trihydroxynaphthalene (2 g.) in ether (30 c.c.) was treated with ethereal diazomethane (from 20 g. of nitrosomethylurea) and left overnight. Removal of the solvent left a dark red oil which largely dissolved when stirred with fresh ether (30 c.c.). The insoluble portion crystallised from light petroleum (b. p. 100—120°) to give yellow crystals, m. p. 208° (120 mg.) (Found: C, 64·7; H, 4·2; N, 11·2. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2; N, 11·5%). This *compound* was insoluble in aqueous sodium hydroxide and gave no ferric chloride colour. The ether-soluble portion was extracted with aqueous sodium hydroxide. Acidification then gave a brown solid, none of which sublimed *in vacuo*, indicating the absence of (IV) and (VI; R = H). No recognisable compound was isolated.

We are grateful to Dr. T. H. Simpson for samples of glucosides.

THE UNIVERSITY, OLD ABERDEEN. [*Received, November 22nd*, 1954.]

The Preparation and Properties of Triphenyl Borate and the Phenoxyboron Chlorides.

By T. COLCLOUGH, W. GERRARD, and M. F. LAPPERT.

[Reprint Order No. 5909.]

Certain differences in properties of phenyl, as compared with alkyl, esters containing boron have been observed. Whereas trialkyl borates (except trimethyl borate) show little tendency to form complexes with tertiary bases, triphenyl borate forms 1 : 1 addition compounds with pyridine, quinoline, and monoethylamine; ability of triphenyl borate to co-ordinate with diethylamine, triethylamine, and tri-*n*-butylamine decreased in that order. Triphenyl borate and the phenoxyboron chlorides were obtained by interaction in appropriate proportions of boron trichloride with phenol. The phenoxyboron chlorides disproportionate reversibly, and form relatively stable co-ordination complexes with pyridine. Distillation of of *tert.*-butyl alcohol with triphenyl borate afforded *iso*butylene and di*iso*-butylene. No interaction between boron trichloride and diphenyl ether was observed.

TRIPHENYL BORATE (Pictet and Geleznoff, *Ber.*, 1903, **36**, 2219; Michaelis and Hillringhaus, *Annalen*, 1901, **315**, 41; Wuyts and Duquesne, *Bull. Soc. chim. Belg.*, 1939, **48**, 77; Gerrard and Lappert, *J.*, 1952, 1486) has now been prepared (83%) more conveniently than hitherto by interaction of boric acid and excess of phenol, the water produced being removed as a phenol–water azeotrope. Scattergood, Miller, and Gammon (*J. Amer. Chem. Soc.*, 1945, **67**, 2150) prepared alkyl borates in a similar way.

Phenyl dichloroboronite $PhO{\cdot}BCl_2$ was obtained by the interaction of boron trichloride with both phenol (*a*) and triphenyl borate (*b*), but it disproportionated readily even at −15° into triphenyl borate and boron trichloride, involving the intermediate formation of the chloroboronate (*b*):

$$PhOH + BCl_3 \longrightarrow PhO{\cdot}BCl_2 + HCl \quad (a)$$

$$2(PhO)_3B \underset{-BCl_3}{\overset{BCl_3}{\rightleftharpoons}} 3(PhO)_2BCl \underset{-2BCl_3}{\overset{2BCl_3}{\rightleftharpoons}} 6PhO{\cdot}BCl_2 \quad (b)$$

By similar procedures, *n-*, *iso-*, and *sec.*-butyl dichloroboronites have been isolated (Gerrard and Lappert, *J.*, 1951, 2545), but these in contrast underwent irreversible decomposition to alkyl chloride, boron trichloride, and boron trioxide.

Diphenyl chloroboronate, prepared by the interaction of boron trichloride (1 mol.) and triphenyl borate (2 mols.), was considerably more stable than the dichloroboronite. Prolonged heating ultimately caused disproportionation into boron trichloride and triphenyl borate, but distillation under reduced pressure afforded a small fraction consisting of a mixture of chloroboronate and dichloroboronite. In addition a very small amount of

dichloroboronite was found. These results indicate that the dichloroboronite is formed as an intermediate step in the disproportionation of the chloroboronate:

$$2(PhO)_2BCl \rightleftharpoons (PhO)_3B + PhO{\cdot}BCl_2$$

$$2PhO{\cdot}BCl_2 \rightleftharpoons (PhO)_2BCl + BCl_3$$

Like *n*-butyl dichloroboronite (Lappert, *J.*, 1953, 667) the phenoxyboron chlorides form stable solid 1 : 1 adducts with pyridine.

From the amount of hydrogen chloride evolved when butyl dichloroboronite was mixed with phenol (*c*), it appeared certain that the mixed ester was formed. Distillation afforded tri-*n*-butyl and triphenyl borate, and the addition of pyridine even at −70° led to the

$$Bu^nO{\cdot}BCl_2 + 2PhOH \longrightarrow Bu^nO{\cdot}B(OPh)_2 + 2HCl \quad . \quad . \quad . \quad . \quad . \quad (c)$$

isolation of tri-*n*-butyl borate and the pyridine–triphenyl borate complex (cf. Thomas, *J.*, 1946, 823, with reference to mixed alkyl borates).

In an attempt to obtain *tert.*-butyl borate, *tert.*-butyl alcohol (2 mols.) was heated with triphenyl borate (1 mol.), but *iso*butylene and di*iso*butylene were formed. With methyl alcohol (3 mols.) and triphenyl borate (1 mol.) alcoholysis (52% in 3 hours at 90°) took place.

No reaction between boron trichloride and diphenyl ether occurred below 25°, whereas with methyl phenyl or ethyl phenyl ether boron trichloride readily caused fission of the (alkyl) C–O bond, forming alkyl chloride and phenyl dichloroboronite (Gerrard and Lappert, *J.*, 1952, 1486, *loc. cit.*). The first step postulated for the fission mechanism was the formation of a co-ordinate B–O link, but with diphenyl ether the nucleophilic character of the oxygen atom is apparently considerably reduced owing to the conjugation of the lone pairs of electrons on the oxygen atom with the phenyl groups. Similarly, diphenyl ether does not form a complex with boron trifluoride (Bowlus and Nieuwland, *J. Amer. Chem. Soc.*, 1931, **53**, 3835; Meerwein and Maier-Hüser, *J. pr. Chem.*, 1932, **134**, 51; Dornte, U.S.P., 2,559,062/1951), by contrast with other ethers.

Co-ordination of Borates with Amines.—Until recently, trialkyl borates were thought to be incapable of forming co-ordination compounds (see, *e.g.*, Sidgwick, "Chemical Elements and their Compounds," Oxford Univ. Press, London, 1950, p. 403). This has since been shown to be substantially correct except for the trimethyl homologue (Goubeau and Link, *Z. anorg. Chem.*, 1951, **267**, 27; Venkataramaraj Urs and Gould, *J. Amer. Chem. Soc.*, 1952, **74**, 2948).

Triphenyl borate forms co-ordination compounds more readily than trialkyl borates, because in the former the $+M$ effect from the oxygen to the aromatic nucleus, assisted by the $-I$ effect of the nucleus, leads to a lower electron density at the boron atom, whereas in the alkyl borates there can be back co-ordination from oxygen to boron (Lewis and Smyth, *J. Amer. Chem. Soc.*, 1940, **62**, 1529).

That the order of nucleophilic strength of the amines which co-ordinate with triphenyl borate is not the same as is found with hydrogen acids, for which $Et_2NH > Et{\cdot}NH_2 > Et_3N >$ pyridine, is probably explained in terms of steric effects (the *F*-strain theory of H. C. Brown *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 32, and many subsequent papers) rather than of polar effects.

Experimental

General Procedures.—Methylene dichloride was used as a solvent because of its high volatility and good solvent properties. Hydrocarbon solvents were less effective, and diethyl ether was avoided in view of its reactivity with boron trichloride.

Analysis for boron in the presence of phenol was carried out by Thomas's method (*J.*, 1946, 820), conversion into trimethyl borate and hydrolysis of the latter to boric acid, estimated acidimetrically in presence of mannitol. The phenoxy-group was estimated by hydrolysis to phenol and iodometric estimation by conversion into the tribromo-derivative. Chlorine was estimated by the Volhard method, and amines in amine complexes by steam-distillation with alkali and titration of the distillate with sulphuric acid to bromophenol-blue.

Preparation and Reactions of Triphenyl Borate.—Triphenyl borate (291 g., 83%), b. p. 157—

158°/0·05 mm., 177—178°/0·5 mm., m. p. 92—93° (Found: B, 3·74; PhO, 96·5. Calc. for $C_{18}H_{15}O_3B$: B, 3·7; PhO, 96·3%), was prepared by heating phenol (560 g., 5·3 mols.) and boric acid (75 g., 1 mol.) at a temperature required for the distillation (through a column) of the 9 : 1 water–phenol azeotrope, b. p. 98—99°. The remaining phenol was removed at low pressure, and the borate was purified by distillation through a lagged and heated column, and by recrystallisation from methylene dichloride.

Hydrolysis. Water (0·55 g., 3 mols.) was added to the borate (2·037 g., 1 mol.) in methylene dichloride (5 ml.) and pentane (10 ml.), and the mixture was heated at 40° for 30 min. The boric acid was filtered off and washed free from phenol by pentane (Found: H_3BO_3, 0·435 g. Calc.: H_3BO_3, 0·435 g.). Evaporation of the solvent afforded a residue of phenol (1·96 g. Calc., 1·97 g.), b. p. 100°/45 mm.

Complexes. Pyridine (6·6 g., 1·1 mols.) was added slowly with shaking to a solution of the borate (20·2 g., 1 mol.) in methylene dichloride (10 ml.) and pentane (20 ml.), and the white precipitate of *pyridine complex* (26·8 g., 100%) (Found: B, 3·02; PhO, 75·3; C_5H_5N, 21·3. $C_{23}H_{20}O_3NB$ requires B, 2·93; PhO, 75·6; C_5H_5N, 21·4%) was filtered off and washed with pentane. The m. p. (148°) was not sharp, because decomposition occurs to the extent of 4% at 120° (0·5 hr.) and 12% at 150° (0·5 hr.). In moist air hydrolysis is complete in 5 days.

Quinoline (3·50 g., 1 mol.) in *n*-pentane (15 ml.) was added to triphenyl borate (7·88 g., 1 mol.) in methylene dichloride (15 ml.) at −60°. The *complex* (10·25 g., 90%) was precipitated at 20° and after being washed with pentane and kept at 2 mm. had m. p. 93—94° (Found: PhO, 65·5; C_9H_7N, 29·3; B, 2·74. $C_{27}H_{22}O_3NB$ requires PhO, 66·5; C_9H_7N, 30·8; B, 2·59%).

Dry ethylamine was passed into the borate (19·9 g., 1 mol.) in methylene dichloride (20 ml.) and pentane (30 ml.), and the white solid *complex* (23·0 g., 100%) was recrystallised from a mixture of the two solvents (Found: B, 3·17; PhO, 82·5; NH_2Et, 14·5. $C_{20}H_{22}O_3BN$ requires B, 3·23; PhO, 83·3; NH_2Et, 13·5%).

Attempts to prepare similarly the corresponding diethylamine complex led to a solid which was low in amine content (Found: B, 2·68; PhO, 80·5; $NHEt_2$, 17·6. Calc. for $C_{22}H_{26}O_3BN$: B, 2·99; PhO, 77·1; $NHEt_2$, 20·2%). Similarly with triethylamine or tri-*n*-butylamine the borate was precipitated and contained only 3—4% of amine. From the pentane washings the greater part of the pure amine was recovered. Similarly also, no evidence of reaction between the borate and di-*n*-butyl sulphide, diethyl ether, dioxan, or tetrahydrofuran was obtained.

Interaction of Phenol with Boron Trichloride.—(*a*) To phenol (29·55 g., 3 mols.) in methylene dichloride (100 ml.) at −80°, boron trichloride (12·3 g., 1 mol.) in methylene dichloride (25 ml.) at −80° was added slowly with shaking. The mixture was then allowed to attain room temperature slowly. The solvent and hydrogen chloride were removed under reduced pressure. The triphenyl borate (25·4 g., 84%) was distilled (b. p. 136—137°/0·1 mm.), and then recrystallised from methylene dichloride (Found: B, 3·82%).

(*b*) By a similar procedure, but with the trichloride (6·3 g., 1 mol.) and phenol (5·0 g., 1 mol.) mixed at −50°, hydrogen chloride (1·95 g., 100% based on: $PhOH + BCl_3 \longrightarrow PhO{\cdot}BCl_2 + HCl$) was obtained at 20° (30 min.), the gas being collected in a tube containing moist potassium hydroxide. On removal of volatile matter at 15°/15 mm. the residue appeared to be a mixture of chloro-esters and triphenyl borate (Found: PhO, 64·1; Cl, 29·2; B, 6·04. Calc. for $C_{12}H_{10}O_2ClB$: PhO, 80·2; Cl, 15·2; B, 4·64. Calc. for $C_6H_5OCl_2B$: PhO, 53·2; Cl, 40·6; B, 6·19%).

Attempted Isolation of Phenyl Dichloroboronite.—(*a*) Addition of triphenyl borate (3·43 g., 1 mol.) in methylene dichloride (10 ml.) to boron trichloride (2·77 g., 2 mols.) at −50°, followed by removal of volatile matter at 15°/15 mm., gave a residue (5·24 g.) consisting of a mixture of the chloro-esters (Found: PhO, 63·0; Cl, 27·8; B, 5·60%). With boron trichloride (3·9 mols.) a similar result was obtained.

(*b*) Triphenyl borate (3·25 g., 1 mol.) in methylene dichloride (20 ml.) was added to boron trichloride (3·48 g., 2·75 mols., *i.e.*, 0·75 mol. excess) at −70°. After the mixture had remained at 20° for 15 minutes to facilitate interaction and permit removal of some excess of boron trichloride, it was again cooled to −70°, and pyridine (3·3 g., 3·75 mols.) in pentane (50 ml.) was added slowly (2 hr.) with shaking. The mixture was stored at 20° for 40 hr. before isolation of the white precipitate of *monopyridine complex* of phenyl dichloroboronite (8·36 g., 94%) (Found: PhO, 34·2; Cl, 27·0; C_5H_5N, 31·0. $C_{11}H_{10}ONCl_2B$ requires PhO, 36·7; Cl, 28·0; C_5H_5N, 31·2%) which for analysis could be separated from accompanying pyridine–boron trichloride by hydrolysis with cold water in which the latter is insoluble (Gerrard and Lappert, *Chem. and Ind.*, 1952, 53). Recrystallisation from methylene dichloride and pentane gave the dichloroboronite complex (m. p. 98—102°) free from pyridine–boron trichloride. After

7 days, no pyridine–boron trichloride had been formed, showing that disproportionation had not occurred (Found : PhO, 34·7; Cl, 30·7; C_5H_5N, 29·6%).

Preparation of Diphenyl Chloroboronate and its Pyridine Complex.—Triphenyl borate (21·7 g., 2 mols.) in methylene dichloride (30 ml.) was added to boron trichloride (4·40 g., 1 mol.) at −70°. After being for 1 hr. at 20° to facilitate interaction in an enclosed system and to prevent loss of boron trichloride, the mixture was cooled to −70°, and pyridine (8·9 g., 3 mols.) in pentane (20 ml.) was added slowly (30 min.). A white precipitate was formed. The solvent was decanted off, and the residue, after being washed with pentane, was the *pyridine complex* of diphenyl chloroboronate (23·48 g., 68%), m. p. 116—118° (Found : PhO, 58·4; C_5H_5N, 24·2; Cl, 10·2; B, 3·40. $C_{17}H_{15}ONClB$ requires PhO, 59·7; C_5H_5N, 25·4; Cl, 11·4; B, 3·48%). The washings afforded a residue (10·5 g., 30·4%) of the crude chloroboronate complex (Found : PhO, 57·6; C_5H_5N, 20·4; Cl, 12·2%).

Disproportionation of Phenyl Dichloroboronite.—Boron trichloride (3·71 g., 3·3 mols., *i.e.*, 1·46 g. excess) at −70° was added to triphenyl borate (2·75 g., 1 mol.) also at −70°. The temperature was then allowed to rise to −15° and the pressure reduced to 0·2 mm. Boron trichloride was collected in tubes containing potassium hydroxide, the tubes being changed at intervals. The excess of trichloride was evolved in the first few minutes, but that formed by disproportionation of the dichloroboronite came over a much slower rate. Since disproportionation became progressively slower, the temperature was increased to 20° after 3·78 hr., and to 100° after 11·37 hr. The results are summarised in the Table. The residue (2·84 g.) consisted mainly of triphenyl borate (Found : PhO, 85·0; Cl, 0·43; B, 5·3%).

Time (hr.)	0·38	1·18	2·62	3·78	4·45	4·79	6·53	11·37	15·22
BCl_3 (g.)	1·46	1·71	1·89	2·02	2·38	2·56	2·94	3·15	3·53
BCl_3 (%)	30·4	46·1	51·0	54·5	64·1	69·0	79·2	84·8	95·1

Disproportionation of Diphenyl Chloroboronate.—(*a*) The chloroboronate (16·30 g., 97·5%) was prepared by the addition of triphenyl borate (14·00 g., 2 mols.) in methylene dichloride (30 ml.) to boron trichloride (2·82 g., 1 mol.) at −70°, solvent subsequently being removed at 20°/30 mm. The product gave a distillate boiling between 52°/0·05 mm., and 116°/0·2 mm. (increase in pressure attributed to trichloride in the system) which was collected in two fractions : (i) 1·86 g., b. p. 52°/0·05 mm. to 104°/0·2 mm. (Found : PhO, 73·0; Cl, 20·7%), (ii) 1·17 g., b. p. 104—116°/0·2 mm. (Found : PhO, 75·5; Cl, 19·7; B, 4·3%), these being mixtures of the two chloro-esters. The residue (13·31 g.) was mainly triphenyl borate (Found : PhO, 95·2; Cl, 0·5; B, 4·3%). Phenyl dichloroboronite (0·68 g.) was collected in an absorption tube containing potassium hydroxide (Found : PhO, 0·35 g. ; Cl, 0·28 g. Calc. for 0·68 g. of $PhO{\cdot}BCl_2$: PhO, 0·36 g. ; Cl, 0·27 g.). Owing to its high volatility, no boron trichloride was collected.

(*b*) Diphenyl chloroboronate (13·35 g.) was prepared by the addition of triphenyl borate (11·10 g., 2 mols.) in methylene dichloride (20 ml.) to boron trichloride (2·25 g., 1 mol.) at −70°. After 1 hr. (20°), the solvent was removed at 10 mm. The chloroboronate was then heated at 100°/100 mm. (6 hr.) and then at 150°/100 mm. (22·5 hr.), an air-condenser being fitted to allow the loss of only boron trichloride from the equilibrium mixture. The trichloride, free from chloro-ester, was collected in tubes containing potassium hydroxide; these were changed at intervals. The results were :

Time (hr.)	3	6	7·5	19·5	28·5
BCl_3 (g.)	0·145	0·156	0·306	0·451	0·458
BCl_3 (%)	6·5	6·9	13·6	20·1	20·4

The residue (12·61 g.) was a mixture of triphenyl borate and diphenyl chloroboronate (Found : PhO, 82·4; Cl, 12·1; B, 4·70%).

*Attempted Preparation of Di-*n*-butyl Phenyl Borate.*—Phenol (9·60 g., 2 mols.) in methylene dichloride (10 ml.) was added to *n*-butyl dichloroboronite (Gerrard and Lappert, *J.*, 1951, 2545) (4·62 g., 1 mol.) at −70°, and the mixture allowed to warm to 15°, whereupon hydrogen chloride [3·68 g., 99·5% according to equation (*c*)] was evolved. The mixture was divided into two parts. From one, solvent was removed at 15°/15 mm., and the liquid *compound* (7·0 g.) (Found : B, 3·94; PhO, 68·9. $C_{16}H_{19}O_3B$ requires B, 4·01; PhO, 68·9%) afforded on distillation tri-*n*-butyl borate (1·55 g., 94%), b. p. 43°/0·002 mm., n_D^{18} 1·4130 (Found : B, 4·3. Calc. for $C_{12}H_{27}O_3B$: B, 4·7%), and triphenyl borate (4·02 g., 97·5%) (Found : B, 3·9; PhO, 95·5%). To the other part (6·5 g., 1 mol.) pyridine (1·9 g., 1 mol.) in methylene dichloride (5 ml.) was added at −70°, and the mixture was kept at 15° for 14 hr. Solvent being removed, the crystalline residue, after being washed with dry ether, afforded the pyridine complex of

triphenyl borate (5·23 g., 87·4%) (Found: B, 3·04; PhO, 75·4; C_5H_5N, 20·3%). The ethereal washings contained pyridine (0·6 g.), tri-*n*-butyl borate (1·17 g.), b. p. 74°/0·7 mm., and triphenyl borate (0·5 g.) (Found: B, 3·9%).

Interaction of tert.-*Butyl Alcohol* (2 *Mols.*) *with Triphenyl Borate* (1 *Mol.*).—Experiments showed that *tert.*-butyl borate could not be isolated, but that *iso*butene and di*iso*butene in approximately equal amounts (total conversion of alcohol into olefin, 96%), each identified as appropriate dibromide, and phenol were the products when triphenyl borate (13·95 g., 1 mol.) was refluxed with *tert.*-butyl alcohol (7·12 g., 2 mols.) at 140—150° for 8 hr.

Interaction of Methanol (3 *Mols.*) *and Triphenyl Borate* (1 *Mol.*).—Methanol (1·56 g., 3 mols.) and triphenyl borate (4·70 g., 1 mol.) were heated for 3 hr. at 90°. Distillation afforded: (i) trimethyl borate and methanol (1·57 g.), b. p. 47—78°/760 mm. (Found: B, 0·089 g. corresponding to 0·82 g. of trimethyl borate), and (ii) phenol (2·20 g. Calc. for 52% conversion into borate, 2·43 g.), b. p. 67°/10 mm. The residue consisted of unchanged triphenyl borate (2·41 g. Calc. for 52% conversion, 2·47 g.) (Found: B, 3·67%), b. p. 147°/0·5 mm. Yields are based on: $3MeOH + (PhO)_3B \longrightarrow (MeO)_3B + 3PhOH$.

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Purpurogallin. Part XII. The Action of Organometallic Compounds on the Tropolones.*

By R. D. HAWORTH and P. B. TINKER.

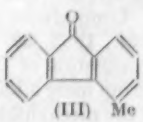
[Reprint Order No. 5913.]

The constitutions of three isomeric methylphenyl*cyclo*heptatrienones, prepared by the action of phenyl-lithium or phenylmagnesium bromide on derivatives of 4-methyltropolone, have been determined by alkaline rearrangement to the methyldiphenylcarboxylic acids, which were identified by conversion into the corresponding methylfluorenones. The results throw considerable light on the mechanism of the reaction of organometallic compounds with tropolones, and new views are advanced to account for the reactions.

IN Part XI* the action of phenylmagnesium bromide on the isomeric methyl ethers (I and II; R = OMe) and dimethylamino-compounds (I and II; R = NMe_2) was shown to give two methylphenyl*cyclo*heptatrienones, m. p. 93° and 99° respectively. By making the assumption that the Grignard reaction occurred by attack at $C_{(1)}$ (path X mechanism: see Part XI) it was suggested that the compounds of m. p. 93° and 99° were 4(?)- and 6(?)-methyl-2-phenyl*cyclo*heptatrienones (II and I; R = Ph) respectively. It was realised that the elucidation of the structures of the two methylphenyl*cyclo*heptatrienones would provide valuable information regarding the mechanism of the Grignard reaction on tropolones, and the present paper reports the results obtained in a further investigation.

(I)

(II)

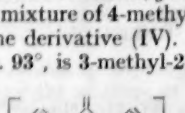


(III)

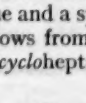
The earlier preparations of the methylphenyl*cyclo*heptatrienones involved a tedious separation of the picrates of the isomeric methyl ethers (I and II; R = OMe) of 4-methyltropolone, and it was hoped to make the *cyclo*heptatrienones more accessible by the reaction of phenyl-lithium on the copper complex of 4-methyltropolone (cf. Doering and Mayer, *J. Amer. Chem. Soc.*, **1953**, **75**, 2387). The reaction was expected to give a mixture of the isomeric *cyclo*heptatrienones (I and II; R = Ph), but to our surprise a

* Part XI, *J.*, 1954, 286.

homogeneous pale yellow methylphenyl*cyclo*heptatrienone, m. p. 134°, was obtained. This new isomer gave an oily hydrochloride, a 2 : 4-dinitrophenylhydrazone, m. p. 138°, and a typical *cyclo*heptatrienone ultra-violet absorption spectrum, but it differed markedly from two isomers of m. p. 93° and 99° respectively. It was therefore apparent that previous views on the reaction of organometallic compounds on tropolones were inadequate, as the two mechanisms involving attack at $C_{(1)}$ or $C_{(2)}$ (path X and path Y mechanisms: see Part XI) cannot account for the formations of these three isomers. The elucidation of their structures has proceeded along similar lines by a study of the alkali-rearrangement products of the three *cyclo*heptatrienones themselves, or of their 2-halogenated derivatives which were prepared by Doering and Mayer's method (*loc. cit.*). In the case of the methylphenyl*cyclo*heptatrienone, m. p. 93°, it was found that definite rearrangement products could not be obtained by the action of alkali. Bromination, however, yielded a pale yellow-green 2-bromo-derivative, m. p. 113°. Attempted acid hydrolysis to the corresponding methylphenyltropolone led to intractable tars which lacked the characteristic tropolone colour reactions and properties, but as in the case of other halogenated *cyclo*heptatrienones (see Seto, *Sci. Rep. Tohôku Univ.*, 1953 **37**, 377) the 2-bromo*cyclo*heptatrienone, m. p. 113°, was readily rearranged to 6-methyldiphenyl-2-carboxylic acid, m. p. 154°, by the action of ethanolic potassium hydroxide. The constitution of this acid was established by cyclisation with concentrated sulphuric acid to 4-methylfluorenone (III), which was identified by comparison with an authentic sample kindly supplied by Dr. M. Orchin (Orchin and Woolfolk, *J. Amer. Chem. Soc.*, 1945, **67**, 122) and also by Clemmensen reduction to a mixture of 4-methylfluorene and a sparingly soluble compound, probably the difluorenylidene derivative (IV). It follows from these experiments that the *cyclo*heptatrienone, m. p. 93°, is 3-methyl-2-phenyl*cyclo*heptatrienone (V).



(IV)



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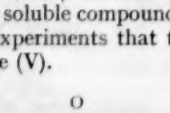
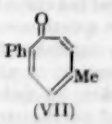


(VI)

This structure (V) is also consistent with the ultra-violet absorption spectrum which differs from those of 2-phenyl*cyclo*heptatrienone (Doering and Hiskey, *ibid.*, 1952, **74**, 5688; Tsuboi, *Bull. Chem. Soc., Japan*, 1952, **25**, 369) and of its two isomers (I) and (VII) (see p. 914). The spectrum of (V) lacks the peak at 265—270 mμ, and has a maximum at 308 mμ (log ε 3·75). Thus it resembles more closely the spectra of *cyclo*heptatrienone and its homologues (Dauben and Ringold, *J. Amer. Chem. Soc.*, 1951, **73**, 896; Doering and Detert, *ibid.*, p. 876; Doering and Hiskey, *loc. cit.*; Nozoe *et al.*, *Proc. Japan Acad.*, 1951, **27**, 477), as would be expected on the assumption that steric interference by the 3-methyl group prevents the phenyl group in (V) from becoming coplanar with the seven-membered ring. As is implicit in the above explanation we regard the spectra of sterically unhindered 2-phenyl*cyclo*heptatrienones as resulting from conjugation of the two rings analogous to that of unhindered diphenyl derivatives (Braude, *Ann. Reports*, 1945, **42**, 125; Gillam and Hey, *J.*, 1939, 1170). Comparison of the spectra of 2-benzyl*cyclo*heptatrienone (Nozoe *et al.*, *Proc. Japan Acad.*, 1953, **29**, 169) and 2-phenyl*cyclo*heptatrienone is sufficient to disprove the opposite contention of Tsuboi (*loc. cit.*) who regards the spectrum of the latter substance as resulting from mere addition of the spectra of benzene and *cyclo*heptatrienone.

The constitution of the methylphenyl*cyclo*heptatrienone, m. p. 99°, was established in a similar manner. Bromination gave a 2-bromo-derivative, m. p. 110°, which was converted into 4-methyldiphenyl-2-carboxylic acid, m. p. 152°, by the action of aqueous-ethanolic potassium hydroxide. The structure of the acid was determined by cyclisation with concentrated sulphuric acid to 2-methylfluorenone (VI), which was identified by comparison of the ketone and its 2 : 4-dinitrophenylhydrazone with authentic specimens kindly supplied by Dr. O. Kruber (*Ber.*, 1932, **65**, 1382). These interconversions prove that the *cyclo*heptatrienone, m. p. 99°, is 5-methyl-2-phenyl*cyclo*heptatrienone (VII), and the conclusion is confirmed by the ultra-violet spectrum.

Bromination in carbon tetrachloride or acetic acid of the methylphenyl*cyclo*heptatrienone, m. p. 134°, prepared from the copper complex of 4-methyltropolone, yielded an oil, which with ethanolic potassium hydroxide gave a small yield of 3-methyldiphenyl-2-carboxylic acid, m. p. 132°, and the same acid was obtained, also in low yield, by the action of ethanolic potassium hydroxide on the unbrominated methylphenyl*cyclo*heptatrienone. On cyclisation with sulphuric acid this diphenylcarboxylic acid gave 1-methylfluorenone (VIII; R = Me), m. p. 98° (Lothrop and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363; Chardonnens and Lieneit, *Helv. Chim. Acta*, 1949, **32**, 2340; Kruber and Raeithel, *Chem.*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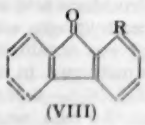
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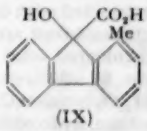
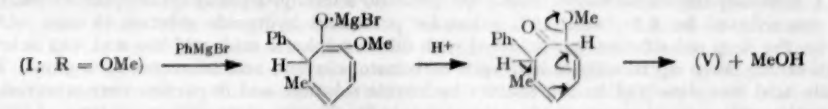
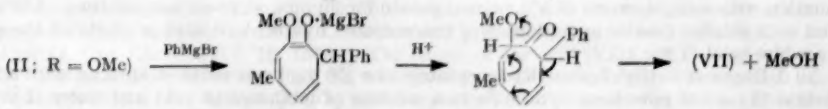

(IX)

Ber., 1954, **87**, 1469), identical with a specimen synthesised by heating 1-methylphenanthraquinone with lead oxide at 220—230° as described for other cases (Cook and Stephenson, *J.*, 1949, 845). These experiments prove that the *cyclo*heptatrienone, m. p. 134°, is 6-methyl-2-phenyl*cyclo*heptatrienone (I; R = Ph). During attempts to improve the preparation of the fluorenone (VIII; R = Me), the impure glycollic acid (IX), obtained by the action of alkali on 1-methylphenanthraquinone, was oxidised with alkaline permanganate to a mixture containing fluorenone-1-carboxylic acid (VIII; R = CO_2H) which clearly arose from further oxidation of 1-methylfluorenone or an intermediate product in its formation. A neutral ketonic compound, $C_{15}H_{10}O_4$, of unknown constitution was also obtained during the permanganate oxidation.

In view of these results previous theories concerning the addition of organometallic compounds to tropolones must be modified. Although the product (I; R = Ph) obtained by the action of phenyl-lithium on the copper complex may be accounted for by one of the mechanisms previously advanced (path X or Y; Part XI, *loc. cit.*) it is clear that the reaction with tropolone ethers results in the attachment of the phenyl group to $C_{(7)}$, probably by 1 : 8-addition to the conjugated system, $-\overset{O}{\overset{\|}{C}}\cdot\overset{OMe}{\overset{|}{C}}CH\cdot CH{:}CH\cdot CMe{:}CH-$, as shown in the following reaction-mechanism schemes:





Nozoe *et al.* (*Proc. Japan Acad.*, 1951, **27**, 419; *Sci. Reports Tohôku Univ.*, 1953, **37**, 388) treated a mixture of hinokitiol methyl ethers with phenylmagnesium bromide and obtained one crystalline product, which on the basis of the above mechanism and the ultra-violet spectrum is probably 2-phenyl-5-*iso*propyl*cyclo*heptatrienone. Similarly the product from 3-bromo-2-methoxy*cyclo*heptatrienone (Nozoe *et al.*, *Proc. Japan Acad.*, 1952, **28**, 142) will be 6-bromo-2-phenyl*cyclo*heptatrienone.

An analogous 1 : 8-addition mechanism will also account for the results of Nozoe, Seto, and Sato (*ibid.*, 1954, **30**, 473) on the action of ammonia on 2-halogenated *cyclo*heptatrienones.

Experimental

*7-Bromo-3-methyl-2-phenyl*cyclo*heptatrienone.*—Bromine (0·41 g.) in carbon tetrachloride (5 c.c.) was added dropwise and with stirring during 2½ hr. to a solution of 3-methyl-2-phenyl-*cyclo*heptatrienone (V) (0·5 g.) [ultra-violet absorption in EtOH: max. at 2330 and 3080 Å

(log ε 4·50, 3·75)], prepared as described in Part XI (*loc. cit.*), in carbon tetrachloride (50 c.c.) containing anhydrous sodium carbonate (0·3 g.) in suspension. After a further 7 hours' stirring, pyridine (0·45 g.) was added and the mixture refluxed for 1 hr. The pyridine hydrobromide was removed by filtration and the yellow solution was washed with dilute sulphuric acid, sodium hydrogen carbonate, and water. Evaporation of the dried carbon tetrachloride solution gave a semisolid product which crystallised from *cyclo*hexane in pale green scales (0·16 g.), m. p. 113° (Found: Br, 29·3. $C_{14}H_{11}OBr$ requires Br, 29·1%).

6-Methyldiphenyl-2-carboxylic Acid.—7-Bromo-3-methyl-2-phenyl*cyclo*heptatrienone (0·1 g.) was refluxed for 7 hr. with 10% ethanolic potassium hydroxide (5 c.c.). After 12 hr. the deep yellow solution was acidified with dilute hydrochloric acid and extracted three times with chloroform. The product was taken up in sodium hydrogen carbonate solution and recovered with chloroform; a buff-coloured solid (0·037 g.) was obtained which separated from *cyclo*hexane–light petroleum (b. p. 60—80°), or aqueous methanol, in white needles, m. p. 154° (Found: C, 78·9; H, 5·9. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%). *6-Methyldiphenyl-2-carboxylic acid* (3 mg.), dissolved in 1% sodium hydroxide solution (0·5 c.c.), was heated on the steam-bath and 5% potassium permanganate solution was gradually added during 3 hr. until a permanent colour was obtained; the solution was clarified with sulphur dioxide and addition of concentrated hydrochloric acid (2 drops) led to the gradual separation in slender needles (1 mg.) of an acid, m. p. 270°, possibly the expected 2-phenyl*iso*phthalic acid, but the quantities available were too small for identification.

4-Methylfluorenone (III).—6-Methyldiphenyl-2-carboxylic acid (6 mg.) in concentrated sulphuric acid (4 drops) was warmed at 40° for 10 min. and, after decomposition with ice, the pale yellow solid (5·5 mg.) was collected. Crystallisation from ethanol yielded 4-methylfluorenone (III) in yellow needles, m. p. and mixed m. p. 88—89°, giving a red precipitate with Brady's reagent. The fluorenone (III) (8 mg.) was refluxed with amalgamated zinc (5 g.) and 5N-hydrochloric acid (15 c.c.) for 16 hr., and the product, isolated with ether, was separated by crystallisation from ethanol into the sparingly soluble *compound*, probably (IV) (4·5 mg.), m. p. 208—209°, and the more soluble 4-methylfluorene, m. p. 69—70° (Orchin and Woolfolk, *loc. cit.*, give m. p. 70—71°).

*7-Bromo-5-methyl-2-phenyl*cyclo*heptatrienone.*—5-Methyl-2-phenyl*cyclo*heptatrienone (VII) (0·5 g.) [ultra-violet absorption in EtOH: max. at 2260, 2670, and 3250 Å (log ε 4·36, 3·75, 4·03)], brominated as described for the isomer on p. 913, gave a yellow oil (0·8 g.), which after sublimation and crystallisation from *cyclo*hexane (charcoal) yielded the *bromocyclo*heptatrienone as small yellow-green prisms (0·2 g.), m. p. 110° (Found: C, 60·9; H, 3·8; Br, 29·4. $C_{14}H_{11}OBr$ requires C, 61·1; H, 4·0; Br, 29·1%).

4-Methyldiphenyl-2-carboxylic Acid.—(i) 7-Bromo-5-methyl-2-phenyl*cyclo*heptatrienone (0·1 g.) was refluxed for 6 hr. with 10% ethanolic potassium hydroxide solution (5 c.c.). After 12 hr. the deep red solution was acidified with dilute sulphuric acid, and the acid was isolated with ether, taken up in sodium hydrogen carbonate solution, and recovered as a gum. The crude acid was dissolved in 2% sodium hydroxide solution, and impurities were removed by oxidation with a slight excess of 5% permanganate for 30 min. at room temperature. Clarification with sulphur dioxide and addition of concentrated hydrochloric acid precipitated the acid as a white solid (1 mg.).

(ii) 7-Bromo-5-methyl-2-phenyl*cyclo*heptatrienone (50 mg.) was refluxed for 5 hr. with a 2N-solution (5 c.c.) of potassium hydroxide in a mixture of methanol (4 vol.) and water (1 vol.). The solution was treated as above, but acidification of the sodium hydrogen carbonate solution gave the acid as a white solid (20 mg.).

Prepared by either method, *4-methyldiphenyl-2-carboxylic acid* crystallised from aqueous methanol in colourless needles, m. p. 152° (Found: C, 79·6; H, 5·7%).

2-Methylfluorenone (VI).—The foregoing acid (7 mg.) was warmed with concentrated sulphuric acid (1 c.c.) for 10 min., and the red solution was decomposed with ice. The yellow precipitate was collected and crystallised from aqueous ethanol or light petroleum (b. p. 60—80°) in yellow needles (1 mg.), m. p. 89—90°, undepressed when mixed with an authentic specimen of 2-methylfluorenone, but a mixture with the 4-methyl isomer (III) melted at 55—60°.

*6-Methyl-2-phenyl*cyclo*heptatrienone* (I; R = Ph).—A solution of phenyl-lithium, prepared from lithium (2 g.) and bromobenzene (22 g.), was filtered through glass wool under nitrogen, and the copper complex (14 g.; crystallised from chloroform) of 4-methyltropolone was added in small portions. After 12 hr., ice and dilute sulphuric acid were added and the mixture was extracted with chloroform. The organic layer was washed with water, and then very dilute aqueous sodium hydroxide, dried, and evaporated under reduced pressure. The residual dark

oil, after being washed several times with small amounts of ether, gave the yellow *cyclo*heptatrienone (I; R = Ph) as a yellow solid (3·5 g.) which crystallised from *cyclo*hexane in slender yellow-green needles, m. p. 133° (Found: C, 85·6, 85·6; H, 6·0, 6·2. $C_{14}H_{12}O$ requires C, 85·7; H, 6·1%). Ultra-violet absorption in EtOH: max. at 2325, 2690, and 3240 Å (log ε 4·40, 3·95, 3·93). *6-Methyl-2-phenylcyclo*heptatrienone (I; R = Ph) was readily soluble in ethanol, moderately so in benzene, and almost insoluble in light petroleum. It dissolved in concentrated hydrochloric acid from which it was recovered by dilution after refluxing for 24 hr., but the hydrochloride was precipitated as a dark viscous oil by passing hydrogen chloride through an ethereal solution of the *cyclo*heptatrienone. The 2:4-*dinitrophenylhydrazone*, prepared in ethanol and precipitated by addition of water, crystallised from a small volume of acetic acid in deep red needles, m. p. 138° (Found: C, 63·9; H, 4·2; N, 14·9. $C_{20}H_{16}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%).

3-Methyldiphenyl-2-carboxylic Acid.—(i) The *cyclo*heptatrienone (I; R = Ph), brominated either as described on p. 913 or in aqueous acetic acid, yielded the 2-bromo-derivative as a brown tar. This tar (0·14 g.) was refluxed for 5 hr. with 10% ethanolic potassium hydroxide (10 c.c.). (ii) The *cyclo*heptatrienone (I; R = Ph) (0·5 g.) was refluxed for 1½ hr. with 8% ethanolic potassium hydroxide (25 c.c.). After dilution the red-brown solution obtained either by method (i) or by method (ii) was acidified and extracted with ether. The acid was removed in sodium hydrogen carbonate solution, recovered, and dissolved in 2% sodium hydroxide solution, and impurities were removed by oxidation with excess of cold 5% permanganate solution for 1 hr. Sulphur dioxide precipitated 3-methyldiphenyl-2-carboxylic acid which crystallised from dilute ethanol in needles, m. p. 132° (Found: C, 79·0; H, 5·8%). Yields were: method (i), 2·5 mg.; method (ii), 2 mg.

1-Methylfluorenone (VIII; R = Me).—(i) The foregoing acid (2·5 mg.) was warmed in concentrated sulphuric acid (2 c.c.) for 15 min. on the steam-bath. The red solution was poured on ice, and the yellow solid collected. (ii) 1-Methylphenanthraquinone (0·1 g.), m. p. 192°, was thoroughly mixed with lead oxide (1 g.) and heated in a metal-bath at 220°. After 3 min., the temperature was lowered to about 150°, and the product sublimed at 8 mm. The orange sublimate (15 mg.) was dissolved in benzene and absorbed on a small column of alumina; unchanged quinone was strongly retained but elution with benzene–*cyclo*hexane (1:2) readily removed the fluorenone (VIII; R = Me).

Prepared by either method, 1-methylfluorenone (VIII; R = Me) separated from light petroleum (b. p. 60—80°) in bright yellow prisms, m. p. 98° (Found: C, 86·3; H, 5·5. Calc. for $C_{14}H_{10}O$: C, 86·5; H, 5·2%) (lit., m. p. 98°).

Fluorenone-1-carboxylic Acid (VIII; R = CO_2H).—Potassium permanganate was gradually added to the cooled solution obtained by refluxing 1-methylphenanthraquinone (0·08 g.) for 7 hr. with excess of 2N-sodium hydroxide. The solution was finally heated on the steam-bath for 2 hr., and a slight permanent excess of permanganate added. The orange yellow solid precipitated by sulphur dioxide was extracted with ether, taken up in sodium hydrogen carbonate solution and recovered; fluorenone-1-carboxylic acid (VIII; R = CO_2H) separated from ethanol in fibrous orange needles (25 mg.), m. p. 190—191°, undepressed on admixture with an authentic specimen kindly supplied by Dr. P. L. Pauson and prepared as described by Koelsch and Steinhauer (*J. Org. Chem.*, 1953, **18**, 1516). The oxime of the acid (VIII; R = CO_2H) had m. p. 229° [Goldschmiedt, *Monatsh.*, 1902, **23**, 886, gives m. p. 230° (decomp.)]. The neutral ethereal solution yielded a *compound*, $C_{15}H_{10}O_4$, which separated from ethanol in yellow needles (10 mg.), m. p. 130—132° (Found: C, 71·3; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%), and gave an orange-red precipitate with Brady's reagent.

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 25th*, 1954.]

Compounds containing Sulphur Chromophores. Part I. The Action of Bases on Heterocyclic Sulphide Quaternary Salts.*

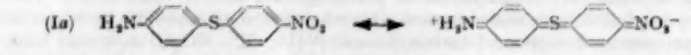
By Edward B. Knott.

[Reprint Order No. 5456.]

It is shown that quaternary salts of type XII (or XLI) on treatment with bases do not give the sulphides (XIII) required as examples of compounds containing chromophoric sulphur. The reactions lead to the elimination of the sulphur atom and the formation of amide type resonators (*e.g.*, XVI). In at least one case a complex disulphide (XXVI) is also formed in low yield. A mechanism of this reaction based on an intramolecular condensation with intermediate episulphide formation is proposed.

Schomaker and Pauling (*J. Amer. Chem. Soc.*, 1939, **61**, 1769) suggested that the low dipole moment of thiophen, compared with that of pyrrole or furan, is the result of contributions by resonance structures in which the sulphur atom expands its octet of electrons to a decet by utilizing its *d*-orbitals. Before their paper the concept of the expansion of the sulphur electron octet had been used to explain the activating influence of a sulphonyl group on an adjacent methylene-carbon atom (Ingold and Jessop, *J.*, 1930, 708; Shriner, Struck, and Jorison, *J. Amer. Chem. Soc.*, 1930, **52**, 2060; Kohler and Larsen, *ibid.*, 1936, **58**, 1448; Connor, Fleming, and Clayton, *ibid.*, p. 1386; Rothstein, *J.*, 1937, 309; 1953, 3991). Since then a number of workers have explained anomalous spectrographic characteristics of certain sulphur compounds on a similar basis (Rothstein, *J.*, 1940, 1550, 1553, 1558; Fehnel and Karmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84, 231, 2889; 1950, **72**, 1292; Koch, *J.*, 1949, 387, 408, 2442; Szmant and Planisek, *J. Amer. Chem. Soc.*, 1950, **72**, 4042; Cilento, *ibid.*, 1953, **75**, 3748; Price and Morita, *ibid.*, p. 4747; see also Longuet-Higgins, *Trans. Faraday Soc.*, 1949, **45**, 173).

Szmant and McIntosh (*J. Amer. Chem. Soc.*, 1951, **73**, 4356) observed a bathochromic shift of 5 mμ on introducing a 4′-amino-group into *p*-nitrophenyl phenyl sulphide, to give (I*a*), and since no similar shift occurred in the diphenyl ether analogues they concluded that this was evidence of contribution by the extreme structure (I*b*). Mangini and Passerini (*J.*, 1952, 1168; see also Koch, *loc. cit.*, p. 387) pointed out, however, that since the benzene rings of (I) are not co-planar there is little likelihood of electronic interaction between them.

(I*a*) 

Apart from the evidence of the above workers, there are also indications in the field of polymethin dyes that a sulphur (or selenium) atom may function as a resonance transmitter in much the same way as a vinylene (·CH:CH·) group. In the symmetrical cyanine series (II*a*) the absorption peaks of dyes from benzothiazole and benzoselenazole lie between these of the analogous dyes from benzoxazole and 2-quinoline. Since contributions to the hybrid by structures such as (II*b*) may be assumed to occur in the quinoline series but not in the benzoxazole dyes the intermediate positions of the peaks of the dyes from benzothiazole and benzoselenazole may indicate contributions by structures such as (II*b*).

Since they involve loss of aromaticity in one of the benzene rings contributions by (II*b*) would not be expected to be as large as those in the case of related thiazoles (III*b*; A = S). On such a basis we should expect that the bathochromic shift observed as we proceed from a symmetrical oxazole dye to the analogous thiazole dye would be greater

* The definitions of a chromophore and an auxochrome or antiauxochrome by Witt and by Dilthey and Witzinger have lead to a certain amount of confusion, as pointed out by Venkataraman ("The Chemistry of Synthetic Dyes," Vol. I, Academic Press Inc., New York, 1952). In this and subsequent papers a resonance system of a dye, or auxochromophoric system (Brooker), is defined as a chain of chromophoric atoms which allow the passage of π-electrons through their orbitals from a $-M$ atom of one auxochrome to a $+M$ atom of another auxochrome.

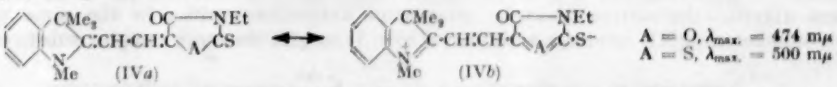
than that shown in the above series. This is found to be true: the shift on proceeding from (III*a*; A = O; Jeffreys, *J.*, **1952**, 4823) ($\lambda_{max.}$ 504 mμ in MeOH) to (III*a*; A = S; Knott, *J.*, 1952, 4099) ($\lambda_{max.}$ 588 mμ) is 84 mμ whilst the related shift in (II; $n = 1$) is 72 mμ (Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *B*, **163**, 138), a difference corresponding to *ca.* 0·05 ev.

(II*a*) (II*b*)

Similarly *mero*cyanines derived from 3-ethyl-2-thio-oxazolid-4-one (IV; A = O) are always lighter in colour than the related dyes from 3-ethyl-2-thiothiazolid-4-one (IV; A = S) (see, *e.g.*, Brooker *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 5332 and earlier papers; Jeffreys, *loc. cit.*). Brooker *et al.* (*loc. cit.*), have shown that the resonance responsible for

(III*a*) (III*b*)

the visible absorption of dyes (IV; A = O) is, energetically, less asymmetric than that for (IV; A = S), so that the deeper colour of the latter is certainly not attributable to an asymmetry effect. It is explicable, however, if such structures as (IV*b*; A = S) contribute to the hybrid since they represent an effective increase in the length of the conjugated path.

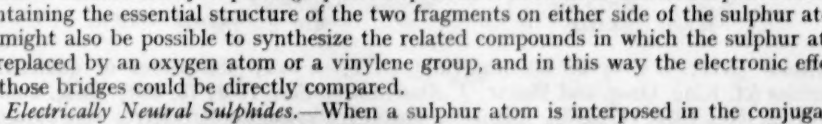


(IV*a*) (IV*b*)

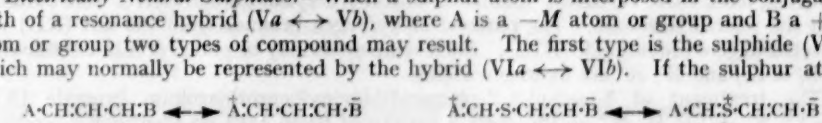
A = O, $\lambda_{max.}$ = 474 mμ
A = S, $\lambda_{max.}$ = 500 mμ

Apart from the work mentioned above on the diphenyl sulphides little has been published on the synthesis of planar molecules in which a sulphur atom has been interposed in a conjugated system between an auxochrome (−*M* group) and an antiauxochrome (+*M* group) (cf. Cilento, *loc. cit.*; with Walter, *J. Amer. Chem. Soc.*, 1954, **76**, 4469). Whether the sulphur atom functions as an insulator or as a conductor in such molecules could be determined by a spectrographic comparison of the molecule with simpler molecules containing the essential structure of the two fragments on either side of the sulphur atom. It might also be possible to synthesize the related compounds in which the sulphur atom is replaced by an oxygen atom or a vinylene group, and in this way the electronic effects of those bridges could be directly compared.

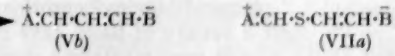
Electrically Neutral Sulphides.—When a sulphur atom is interposed in the conjugated path of a resonance hybrid (V*a* ⟷ V*b*), where A is a −*M* atom or group and B a +*M* atom or group two types of compound may result. The first type is the sulphide (VI*a*) which may normally be represented by the hybrid (VI*a* ⟷ VI*b*). If the sulphur atom



(V*a*) (V*b*) (VII*a*) (VII*b*)



(VI*a*) (VI*b*) (VII*c*) (VII*d*)

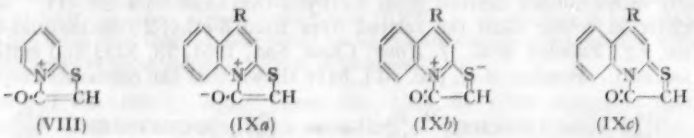


(VI*c*) (VI*d*)

expands its octet then the hybrid may more truly be represented by (VI*a* ⟷ VI*b*), and (VI*c*) will be an important contributing structure. The second type results when the sulphur atom is interposed between carbon atoms adjacent to those divided by sulphur in (VI). This gives what would be called a mesoionic sulphide which is represented by (VII*a* ⟷ VII*b*) if the sulphur does not expand its octet. In such cases types (VI*a*) and (VII*a*) are distinct. If the *d*-orbitals are utilized then (VII*a*) is represented by (VII*a* ⟷ VII*d*) and the distinction between the hybrids (VI) and (VII) is reduced.

This present paper is concerned with the attempted synthesis of sulphides of type (VII).

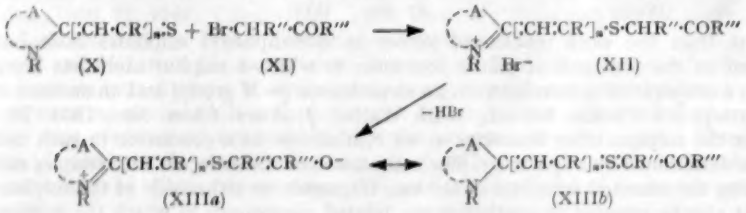
Koenigs and Geisler Compounds.—Duffin and Kendall (*J.*, 1951, 734) showed conclusively that the product obtained by Koenigs and Geisler (*Ber.*, 1924, **57**, 2076) by heating (2-pyridylthio)acetic acid with acetic anhydride was the compound (VIII). They also made related compounds (IX) in the quinoline series and suggested that the intense, yellow colour of the solutions of these dyes was due to contributions by a number of resonance structures including (IX*b*) in which the sulphur *d*-orbitals are involved. If such an expansion of the sulphur octet does occur, then the resonance hybrid may more truly be represented by (IX*a* ⟷ IX*c*).



(VIII) (IX*a*) (IX*b*) (IX*c*)

The compound (IX; R = Me), which Duffin and Kendall found to be the most stable of the series, has been examined spectrographically in a number of solvents. These results will be described in Part IV of this series.

Open-chain Analogues of the Compound (VIII).—The synthesis of open-chain benzothiazole analogues of (VIII) [*i.e.*, (XIII)] was then investigated. It is known (Fischer, *Ber.*, 1902, **35**, 3674; Rassow, Döhle, and Reim, *J. pr. Chem.*, 1916, **93**, 183; Hamer and Rathbone, *J.*, 1943, 243) that alkyl halides react with *N*-substituted cyclic thiones to form alkylthio-derivatives of cyclic quaternary ammonium salts. In the same way α-bromo-ketones (XI) condense with (X; $n = 0, 1$) to give the more complex substituted



alkylthio- (XII; $n = 0$) or alkylthiovinyl (XII; $n = 1$) derivatives of quaternary bromides (cf. King, Ozog, and Moffat, *J. Amer. Chem. Soc.*, 1951, **73**, 300; Ozog, Comte, and King, *ibid.*, 1952, **74**, 6225). Similarly, unstable alkylseleno-derivatives were obtained from the related selenones. The removal of hydrogen bromide from the salt (XII) was expected to give the sulphide (XIII). Such compounds may be planar if A is a heteroatom (O, S, or Se) and R′, R″ are hydrogen atoms.

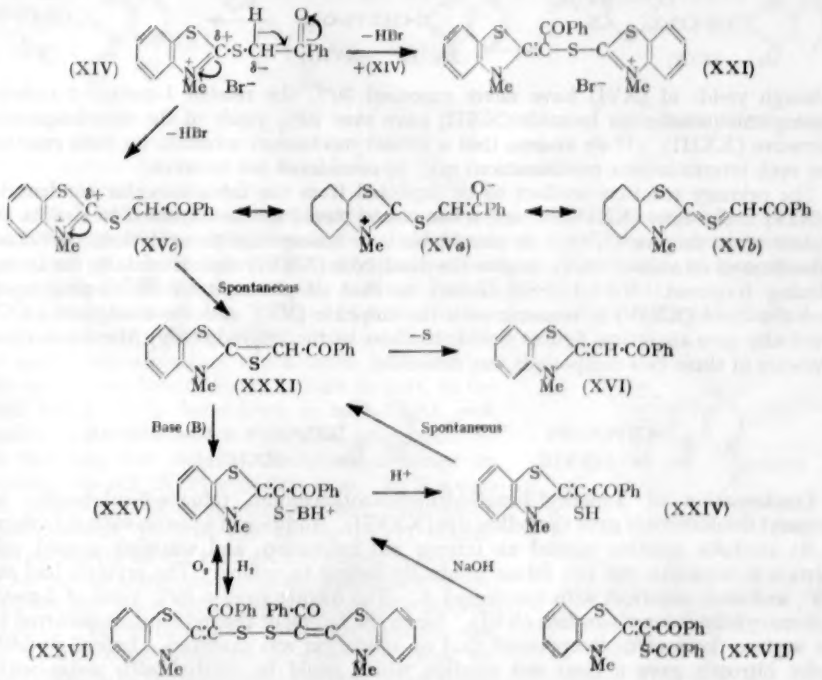
The treatment of 3-methyl-2-2′-phenacylthiovinylbenzothiazolium bromide (XII; $n = 1$; R′, R″ = H, R‴ = Ph) with a variety of bases gave no identifiable products. Similar treatment of the salt (XII; $n = 0$) gave crystalline products in all cases except where the heterocycle was a 1-alkylpyridinium nucleus.

In the first instance, 3-methyl-2-phenacylthiobenzothiazolium bromide (XIV) was treated with triethylamine in alcoholic solution to give bright yellow needles, the analysis of which indicated that the molecule contained one atom of sulphur less than that required for the sulphide (XV). It showed no depression in melting point with an authentic specimen of 3-methyl-2-phenacylidenebenzothiazoline (XVI) prepared by Brooker and White's procedure (U.S.P. 2,112,139) although its melting point (170—174°) was lower than that of (XVI) (176°) and it was bright yellow whilst (XVI) was cream-coloured. Careful extraction of the yellow needles with warm ethanol left undissolved a small amount of yellow grains which, after purification, formed glossy yellow flakes, m. p. 263° (Compound A), giving analytical figures agreeing well with those required for the sulphide (XV). The removal of compound A raised the m. p. of the main product to the correct

value for the ketone (XVI). Further experiments on the removal of hydrogen bromide from (XIV) gave either only ketone (XVI) in yields of up to 50% or, when inorganic bases were used, in addition up to 12% of compound A and traces of a second yellow compound, m. p. 217°. Analysis of the compound, m. p. 217°, indicated that it might be the thione corresponding with (XV). The fate of the missing sulphur was partly accounted for by the isolation of nacreous (μ-)sulphur.

Heating a pyridine solution of compound A with aqueous sodium hydroxide caused the yellow colour to deepen to orange before fading, and a high yield of ketone (XVI) was obtained.

If compound A was the required sulphide (XV) it might be expected that the addition of hydrogen bromide to it would give the original quaternary bromide (XIV). The

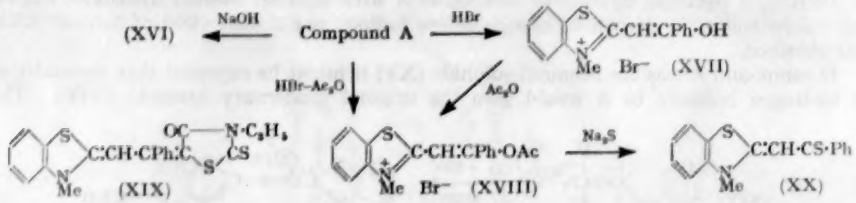


product obtained, however, was 2-α-hydroxystyryl-3-methylbenzothiazolium bromide (XVII), the same product being obtained by the addition of hydrogen bromide to the ketone (XVI). Its structure was proved by acetylation to give the 2-α-acetoxystyryl compound (XVIII), which with 3-allylrhodanine and with sodium sulphide yielded the dye (XIX) and thio-ketone (XX) respectively. Treatment of compound A with hydrogen bromide in acetic anhydride gave the acetate (XVIII) directly and elementary sulphur. Although the loss of sulphur from compound A in the above reactions seemed extraordinary it did indicate that a similar type of reaction could account for the high yields of ketone (XVI) in the primary reaction.

It is known (Kendall, B.P. 426,718) that 2-alkylthiobenzothiazolium salts and similar derivatives of other heterocycles contain an electrophilic $C_{(2)}$ atom which condenses with the nucleophilic methylene carbon atom of ketomethylene compounds under the influence of bases to yield *mero*cyanines, with the elimination of an alkanethiol. In the 3-alkyl-2-phenacylthiobenzothiazolium salt molecule (XIV) reactive centres of both types are present. The treatment of such molecules by bases may result, therefore, not only in

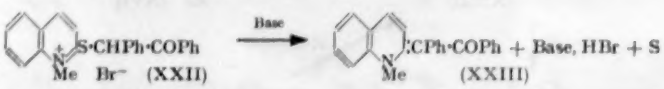
simple elimination of hydrogen bromide, but also in either an intermolecular or an intramolecular condensation, on the assumption in the latter case that the reactive centres may approach each other sufficiently closely for bond formation between them to occur.

By analogy with *mero*cyanine formation the primary intermolecular reaction product would be (XXI) which might conceivably break down to give 3-methyl-2-phenacylidenebenzothiazoline (XVI) in a maximum yield of 50% based on starting material (XIV).



Although yields of (XVI) have never exceeded 50% the related 1-methyl-2-α-phenylphenacylthioquinolinium bromide (XXII) gave over 90% yields of the dihydroquinoline derivative (XXIII). If we assume that a similar mechanism accounts for both reactions, then such intermolecular condensations may be considered not to occur.

The primary reaction product to be expected from the intramolecular condensation of (XIV) is the thiol (XXIV). Such a compound would not be expected to lose its thiol sulphur atom to give (XVI). It should be very susceptible to oxidation, particularly in the form of its anion (XXV), to give the disulphide (XXVI) since it contains the strongly reducing fragment –NR·C:CH·SH similar to that of photographic developing agents. Since the thiol (XXIV) is isomeric with the sulphide (XV), and the disulphide (XXVI) would also give analytical figures similar to those of the sulphide (XV), the unambiguous syntheses of these two compounds was desirable.

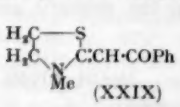


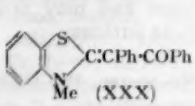
Condensation of 3-methyl-2-methylthiobenzothiazolium toluene-*p*-sulphonate with phenacyl thiolbenzoate gave the yellow dye (XXVII). Addition of aqueous sodium hydroxide to its alcoholic solution caused an intense red coloration, and warming caused yellow crystals to separate, the red colour gradually fading to yellow. The crystals had m. p. 263°, and were identical with compound A. The filtrate gave a 50% yield of 3-methyl-2-phenacylidenebenzothiazoline (XVI). Since the fading of the red solution occurred from the surface downwards it appeared that an oxidation was involved. Indeed hydrolysis under nitrogen gave a clear red solution which could be diluted with water without precipitation. The red colour is therefore ascribed to the thiol anion of (XXV) which forms an insoluble orange silver salt. Persulphate at once discharged the red colour and precipitated compound A in 80% yield. There is therefore no doubt that the latter is the disulphide (XXVI). It is readily reduced to the red thiol salt with sodium sulphide. Low molecular weights (Rast) found for the disulphide may be due to partial dissociation to the thiyl radicals (cf. Cutforth and Selwood, *J. Amer. Chem. Soc.*, **1948**, **70**, 278), which may also account for the bright orange colour of the molten disulphide.

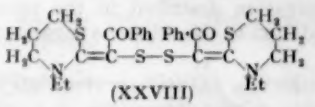
When the red solution obtained by hydrolysis of (XXVII) under nitrogen was neutralized with acetic acid, hydrogen sulphide was evolved and the precipitate contained the disulphide (XXVI) (8%) and 3-methyl-2-phenacylidenebenzothiazoline (XVI) (60%).

In one other case the treatment of a quaternary salt, 3-ethyl-4 : 5-dihydro-2-phenacylthio-1 : 3-thiazinium bromide, with triethylamine gave a product, which is probably the analogous disulphide (XXVIII). The red crystals obtained by treating 1-methyl-2-phenacylthioquinolinium bromide with triethylamine were not identified. The ketones (XXIX) and (XXX) were the sole products isolated from the treatment of the related quaternary salts (XII) with triethylamine.

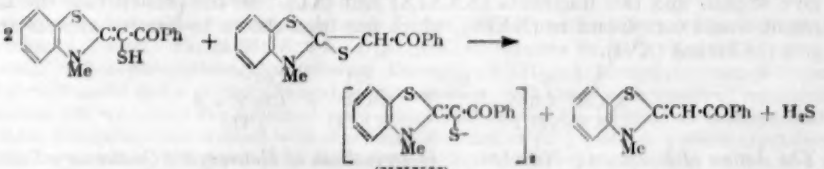
The seleno-analogue of (XXII) with triethylamine gave a small yield of the same dye (XXIII) as was obtained from (XII).


(XXIX)


(XXX)

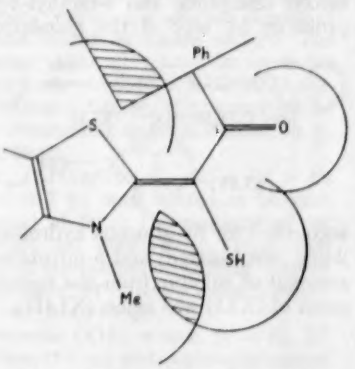

(XXVIII)

Possible Mechanisms of the Reactions.—The first step in the reaction of the quaternary cation (XIV) with a base is assumed to be the removal of a proton from the methylene-carbon atom. This would give (XV*c*) which is an excited structure of the sulphide resonance hybrid (XV*a* ⟷ XV*b*). If the angle of the chain sulphur bonds is 100° the distance between the negatively charged carbon atom and the electrophilic $C_{(2)}$-atom is

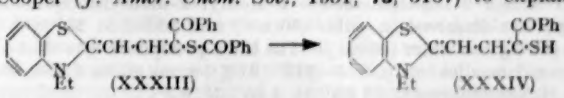

(XXXII)

ca. 2·75 Å but, because of the electrostatic attraction between these carbon atoms and the flexibility of the sulphur bonds, this distance may at times be considerably less. The formation of a bond by charge neutralization between these atoms to give the *spiro*-episulphide (XXXI) is thus feasible (see also Part IV).

If the quaternary salt (XIV) is treated with aqueous sodium hydroxide the red thiol anion is formed (giving a 25% yield of disulphide on oxidation), a reaction which could indicate that the episulphide breaks down, at least in part, to the thiol anion. This breakdown is only slight with weaker bases such as triethylamine, as is indicated by the very low yield of disulphide obtained on treating the salt (XIV) with this base. In this case the splitting off of elementary sulphur, possibly by base catalysis, to give the ketone (XVI) occurs. The instability of the thiol (XXIV) itself is believed to be due to steric hindrance to coplanarity of the thiol-sulphur atom with the benzothiazoline nucleus (Figure). The evolution of hydrogen sulphide and the simultaneous formation of some disulphide on neutralization of the solution of the thiol anion seems to indicate a reductive process, possibly of the type giving rise to the compound (XXXII), above. In accordance, the vinylogue of (XXIV), namely (XXXIV), obtained by hydrolysis of the dye (XXXIII), does not suffer from steric hindrance to planarity and, in the absence of oxygen, is stable.



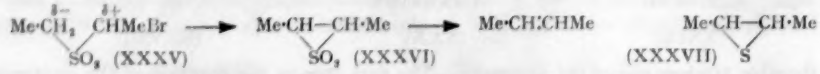
The hypothesis of the formation of episulphides is similar to that put forward by Bordwell and Cooper (*J. Amer. Chem. Soc.*, 1951, **73**, 5187) to explain the conversion


(XXXIII) (XXXIV)

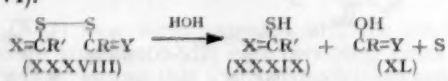
of the bromo-sulphone (XXXV) by alkali at 90—100° into but-2-ene and sulphur dioxide (Ramberg and Bäcklund, *Arkiv Kemi Min., Geol.*, 1940, **13**, *A*, No. 27).* Loss of sulphur dioxide from such episulphones (XXXVI) has been reported by Staudinger and Pfenninger

* Parham and Traynelis (*J. Amer. Chem. Soc.*, 1954, **76**, 4960) have shown that 2 : 5-diphenyl-1 : 4-dithiin is converted into 2 : 4-diphenylthiophen at 190° with the elimination of elementary sulphur and have postulated the intermediate formation of an episulphide.

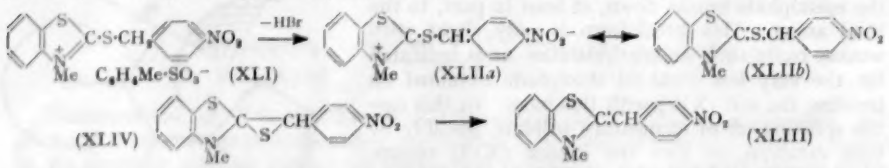
(*Ber.*, 1916, **49**, 1941). Loss of sulphur from the sulphide (XXXVII) on storage (Price and Kirk, *J. Amer. Chem. Soc.*, 1953, **75**, 2396) may also be related to the sulphur elimination described in the present paper and may not require the primary aerial oxidation to the sulphone suggested by these authors.



The mechanism of the decomposition of the disulphide (XXVI) by sodium hydroxide or hydrogen bromide is obscure. Fromm (*Annalen*, 1906, **348**, 144) collected evidence to show that disulphides (XXXVIII), in which the carbon atoms to which the disulphide group is bonded are unsaturated, are decomposed by alkali, or in some cases by water, to give sulphur and two fragments (XXXIX) and (XL). In the present case the thiol fragment would correspond to (XXIV), which has been shown to lose its sulphur atom to give the ketone (XVI).



The Action of Bases on p-*Nitrobenzylthio-derivatives of Heterocyclic Quaternary Salts.*—After failure to obtain open-chain sulphides of type (VII) in which the group B contained a keto-group, attention was turned to related compounds in which group B contained a nitro-group. Condensation of *p*-nitrobenzyl chloride with 2-mercaptobenzothiazole gave 2-*p*-nitrobenzylthiobenzothiazole, which on quaternization gave the salt (XLI). Removal of toluenesulphonic acid from the latter by pyridine or aqueous-alcoholic triethylamine did not give the sulphide (XLII*a* ⟷ *b*). Two products were isolated, di-*p*-nitrobenzyl disulphide and 3-methyl-2-*p*-nitrobenzylidenebenzothiazoline (XLIII), the latter probably by way of the *spiro*episulphide (XLIV). The disulphide formation may be



accounted for by aqueous hydrolysis of the quaternary salt, giving 3-methylbenzothiazol-2-one (not isolated) and *p*-nitrotoluene-ω-thiol the latter being oxidized aerially, or in the removal of sulphur from the episulphide. The product isolated from the pyridine treatment of (XLI) was again (XLIII).

Experimental

Microanalyses were partly by Mr. C. B. Dennis.

Heterocyclic Thiones (X; $n = 0$).—These were obtained (cf. Sexton, *J.*, 1939, 470) by treating the 2-alkylthio-derivative of the heterocyclic quaternary salt with aqueous sodium sulphide, best at room temperature. The related selenones were obtained similarly by using aqueous sodium selenide (cf. Michaelis and Holken, *Annalen*, 1904, **331**, 251).

1 : 2-*Dihydro*-1-*methyl*-2-*selenoquinoline*.—1-Methyl-2-methylthioquinolinium toluene-*p*-sulphonate (18·0 g.) was dissolved in water (50 c.c.) and added at 20° to a filtered solution of sodium selenide (12·5 g.) in water (50 c.c.). The thick precipitate was washed with water and obtained as orange-red needles, m. p. 115—116° (91%), from ethanol (Found: C, 54·15; H, 4·05; N, 6·1. $C_{10}H_9NSe$ requires C, 54·05; H, 4·05; N, 6·3%).

3-*Methyl*-2-*selenobenzothiazoline*, obtained similarly (87%), formed pale yellow flakes, m. p. 108—110°, from ethanol (Found: C, 42·35; H, 3·25; N, 6·2; S, 14·3. C_8H_7NSSe requires C, 42·15; H, 3·1; N, 6·15; S, 14·05%).

3-*Methyl*-2-*phenacylthiobenzothiazolium Bromide* (XIV).—3-Methyl-2-thiobenzothiazoline (1·8 g., 0·01 mole) and phenacyl bromide (2·0 g., 0·01 mole) were fused together for 10 min. on the steam-bath. The solid cake was dissolved in ethanol (10 c.c.), and dry ether was run

in slowly to give 2·45 g. (64·5%) of the *thiazolium bromide*. This formed cream-coloured needles, m. p. 121°, from ethanol (Found: C, 50·4; H, 4·7; Br, 19·1; S, 15·25. $C_{16}H_{14}ONBrS_2,C_2H_5{\cdot}OH$ requires C, 50·7; H, 4·7; Br, 18·8; S, 15·05%).

1-*Methyl*-2-*phenacylthioquinolinium bromide*, obtained similarly (88%), formed similar needles, m. p. 179° (orange melt), from ethanol–ether (Found: Br, 19·15; S, 7·6. $C_{18}H_{16}ONBrS,C_2H_5{\cdot}OH$ requires Br, 19·05; S, 7·6%).

3-*Methyl*-2-*phenacylthiothiazolinium bromide* obtained by the above method (see also Batty and Weedon, *J.*, 1949, 786) from 3-methylthiazolidin-2-thione in 82% yield, formed white crystals, m. p. 117—120°, from ethanol (Found: Br, 23·8; S, 19·4. $C_{12}H_{14}ONBrS$ requires Br, 24·1; S, 19·3%).

3-*Ethyl*-**4** : 5-*dihydro*-2-*phenacylthio*-**1** : 3-*thiazinium bromide* was obtained from the related thione (Hamer and Rathbone, *loc. cit.*) as a tar which crystallised from ethanol (80% yield) and formed light brown needles, m. p. 135°, from ethanol–ether (Found: Br, 22·1; S, 17·75. $C_{14}H_{18}ONBrS_2$ requires Br, 22·25; S, 17·8%).

1-*Methyl*-2-*phenacylthiopyridinium bromide* formed yellow needles (93%), m. p. 180—181°, from ethanol (Found: Br, 24·55; S, 9·7. $C_{14}H_{14}ONBrS$ requires Br, 24·7; S, 9·9%).

1-*Methyl*-2-α-*phenylphenacylquinolinium Bromide* (XXII).—1-Methylquinoline-2-thione (1·75 g., 0·01 mole) and α-phenylphenacyl bromide (2·75 g., 0·01 mole) were dissolved separately in benzene (25 c.c.), and the solutions were mixed and heated for 15 min. on a steam-bath. The thick precipitate was washed with ether and obtained in 62% yield as a white crystalline powder, m. p. 175—177°, from ethanol–ether (Found: C, 62·1; H, 5·85; Br, 14·8; S, 6·1. $C_{24}H_{20}ONBrS,2C_2H_5{\cdot}OH$ requires C, 61·9; H, 5·9; Br, 14·75; S, 5·9%).

2-*Phenylcarbamylmethylthio*-1-*methylquinolinium bromide* (XII; $n = 0$, R = Me, R″ = H, R‴ = NHPh).—1-Methylquinoline-2-thione (3·5 g.) and ω-chloroacetanilide (3·4 g.) were fused together on the steam-bath for 5 min. The solid salt (5·3 g., 77%) formed yellow aggregates, m. p. 216° (red melt; effervesces), from methanol–ether (Found: C, 62·3; H, 5·05; N, 8·0; Cl, 9·95; S, 9·15. $C_{18}H_{17}ON_2ClS$ requires C, 62·75; H, 4·95; N, 8·15; Cl, 10·3; S, 9·3%).

3-*Ethyl*-2-*thioformylmethylenebenzothiazoline* (X; $n = 1$, R′ = H).—2-2′-Acetanilidovinyl-3-ethylbenzothiazolium iodide (45·0 g.) was suspended in acetone (100 c.c.), a solution of sodium sulphide nonahydrate (48·0 g.) in water (50 c.c.) added, and the whole shaken at 30°. The orange solution was filtered after 30 min. and diluted with water (500 c.c.). A red tar separated which gradually crystallised. From ethanol (400 c.c.) there was obtained a total of 18·2 g. (82·5%) of red crystals. This compound was dissolved in benzene, filtered, and reprecipitated by means of light petroleum (b. p. 60—80°). It was finally obtained as magenta needles, m. p. 87°, from ethanol (Found: S, 28·7. $C_{11}H_{11}NS_2$ requires S, 29·0%).

3-*Ethyl*-2 : 2′-*phenacylthiovinylbenzothiazolium Bromide* (XII; $n = 1$, R′ = R″ = H, R‴ = Ph).—3-Ethyl-2-thioformylmethylenebenzothiazoline (2·2 g.) was treated in benzene (20 c.c.) with phenacyl bromide (2·0 g.) in benzene (10 c.c.) at 20°. The precipitated tar crystallised and was collected, washed with water and ether, and dissolved in hot ethanol (20 c.c.). The required quaternary *salt* (3·2 g., 68·5%), which crystallised on chilling, formed pale yellow needles, m. p. 150—160° (softened and became orange at 94°), from ethanol (Found: Br, 17·6; S, 14·0. $C_{19}H_{18}ONBrS_2,C_2H_5{\cdot}OH$ requires Br, 17·4; S, 13·75%).

3-*Ethyl* 2-(2-α-*phenylphenacylthiovinyl*)*benzothiazolium Bromide* (XII; $n = 1$, R′ = H, R″ = R‴ = Ph).—3-Ethyl-2-thioformylmethylenebenzothiazoline (2·2 g.) and α-phenylphenacyl bromide (2·75 g.) were heated in benzene (10 c.c.) for 15 min. on a steam-bath. A tar separated and solidified during this time. Ether (30 c.c.) was added and the solid *bromide* was collected and washed with acetone. It (4·4 g., 89%) formed yellow crystals, m. p. 184° (effervesces and turns magenta) from ethanol (Found: Br, 15·95; S, 12·6. $C_{25}H_{22}ONBrS_2$ requires Br, 16·15; S, 12·9%).

Action of Bases on the Sulphide (XII; $n = 0$) *and its Analogues*.—(a) 3-*Methyl*-2-*phenacylthiobenzothiazolium bromide* (i) The quaternary salt (1·35 g.) was dissolved in pyridine (15 c.c.) by warming to 50°. The solution was allowed to cool and water (70 c.c.) was added. A yellow tar was precipitated which gradually set to a sticky solid. The aqueous layer which gave no sulphide reaction was decanted and the residual 3-methyl-2-phenacylidenebenzothiazoline (XVI) washed with cold ethanol. It (0·25 g., 29·5%) formed pale yellow flakes, m. p. 176°, from benzene (Found: C, 71·5; H, 4·8; N, 5·1; S, 12·1. Calc. for $C_{16}H_{13}ONS$: C, 71·8; H, 4·85; N, 5·25; S, 12·0%). Van Dormael and Ghys (*Bull. Soc. chim. belges*, 1950, **59**, 593) give m. p. 175—176°. A mixed m. p. with a sample obtained by Brooker and White's method (*loc. cit.*) was 176°.

(ii) The quaternary salt (4·25 g., 0·01 mole) was dissolved in ethanol (50 c.c.) and

triethylamine (3 c.c.; 0·02 mol.) was added at 25°. After 2 min. water was run in until the solution was faintly turbid and the whole was chilled overnight. Crystals (1·8 g.) which separated formed bright yellow needles, m. p. 170—174°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 71·1; H, 4·8; N, 5·1; S, 12·7%). Cautious extraction with warm ethanol left a little insoluble yellow residue. The ethanol on concentration gave 1·25 g. (47·0%) of the compound (XVI), m. p. 176°. The insoluble *di-*[α-(*3-methylbenzothiazolinylidene*)*phenacyl*] *disulphide* (XXVI) (0·06 g.) formed glossy, yellow flakes, m. p. 263°, from pyridine–ethanol (Found: C, 64·25; H, 4·2; N, 4·7; S, 21·75%; *M*, 274, 296. $C_{32}H_{24}O_2N_2S_4$ requires C, 64·45; H, 4·05; N, 4·7; S, 21·5%; *M*, 596). Its pyridine solution is instantly reduced to the orange-red sodium salt (XXV) with sodium sulphide.

(iii) The finely ground quaternary salt (20 g.) was stirred under benzene (250 c.c.). Sodium hydrogen carbonate (25 g.) and water (50 c.c.) were added and the whole was stirred rapidly at 25° for 1 hr. The yellow benzene layer then contained a pale yellow solid, and the original quaternary salt had disappeared. Nine such batches were united and the suspended solid (A) was collected. The benzene layer of the filtrate was dried and concentrated to 100 c.c. (B). The solid (A) was extracted with boiling ethanol (800 c.c.), leaving an insoluble yellow residue (C). The ethanol extract yielded the ketone (XVI) (23 g.) on concentration and a further 32 g. were obtained from the benzene solution (B) (total yield 44%). The yellow residue (C) was extracted with boiling benzene (4 l.) (D) to leave undissolved a bright yellow powder (0·45 g.), m. p. 215°. It formed bright yellow crystals, m. p. 217°, from pyridine–ethanol (Found: C, 61·55; H, 4·5; N, 4·6; S, 29·45. $C_{32}H_{24}N_2S_6$ requires C, 61·15; H, 3·8; N, 4·45; S, 30·6%). The compound may thus be the *disulphide* corresponding to (XXVI). Concentration of the benzene extract (D) yielded 11·2 g. (8%) of the disulphide (XXVI), m. p. 263°, after recrystallization from pyridine–ethanol.

The benzene filtrates (B) were concentrated further, yielding nacreous sulphur (1·6 g.), m. p. 112°, and 3-methylbenzothiazolin-2-thione (6·5 g.), m. p. 87°.

(iv) Quaternary salt (2·15 g.), dissolved in ethanol (25 c.c.), was added at 25° to a solution of sodium (0·6 g.) in ethanol (25 c.c.). After 5 min. a slurry of potassium persulphate (2 g.) in water (20 c.c.) was added. The colour changed to light orange and yellow crystals separated. After chilling, the crystals were collected and washed with water and ethanol. The disulphide (XXVI) (0·65 g., 43·5%) formed glossy yellow flakes, m. p. 263°, from pyridine–ethanol, identical with the product obtained as under (iii).

(b) *1-Methyl-2-phenacylthioquinolinium bromide.* The quaternary salt (3·75 g.) was dissolved in ethanol (20 c.c.) and cooled to 0°. Triethylamine (2·5 c.c.) was added and the temperature allowed to rise to 20°. The precipitated substance (2·6 g.) formed red crystals, m. p. 192°, from pyridine–ethanol (Found: C, 68·05; H, 4·55; N, 5·35; S, 17·25%). It was not identified.

(c) *3-Methyl-2-phenacylthiothiazolinium bromide.* The quaternary salt (3·3 g.) was suspended in water (10 c.c.) and triethylamine (1·5 c.c.) was added. A thick yellow tar separated and became semi-solid. From ethanol (twice) there was obtained 0·3 g. (13·5%) of pale yellow needles, m. p. 125°, of *3-methyl-2-phenacylidenethiazolidine* (XXIX) (Found: C, 65·0; H, 6·1; N, 6·4; S, 14·65. $C_{12}H_{13}ONS$ requires C, 65·75; H, 5·95; N, 6·4; S, 14·6%).

(d) *3-Ethyl-4:5-dihydro-2-phenacylthio-1:3-thiazinium bromide.* The quaternary salt (3·6 g.) was suspended in ethanol (20 c.c.), triethylamine (3 c.c.) was added, and the solid was dissolved with stirring. Triethylamine hydrobromide and a chrome-yellow solid slowly separated. The solids were collected after 2 days, and the triethylamine hydrobromide was washed out with ethanol and water. The yellow residual (?) *di-*[α-(*3-ethyltetrahydro-2-thiazinylidene*)*phenacyl*] *disulphide* (XXVIII) (0·8 g.) formed an orange-yellow crystalline powder, m. p. 188°, from pyridine–ether (Found: C, 60·3; H, 5·75; N, 4·9; S, 23·05. $C_{28}H_{32}O_2N_2S_4$ requires C, 60·4; H, 5·75; N, 5·05; S, 23·0%).

(e) *1-Methyl-2-α-phenylphenacylquinolinium bromide* (XXII). (i) The quaternary salt (2·5 g.) was covered with ethanol (15 c.c.) and triethylamine (1 c.c.) added. The dye (1·55 g., 100%) which separated as the quaternary salt dissolved was obtained in 91% yield as orange plates, m. p. 218°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 85·3; H, 5·5; N, 4·25. $C_{24}H_{19}ON$ requires C, 85·5; H, 5·65; N, 4·15%). It is 1:2-*dihydro-1-methyl-2-α-phenylphenacylquinoline* (XXIII). The m. p. showed no depression when the dye was mixed with a sample prepared by condensing 1-methyl-2-methylthioquinolinium toluene-*p*-sulphonate with deoxybenzoin in alcoholic triethylamine.

(ii) The quaternary salt (5·4 g.) was dissolved in pyridine (50 c.c.) at 55° in 5 min. After a further 5 min., water (20 c.c.) was slowly run in, the dye (XXIII) crystallising in 90%

yield. On concentration the filtrate yielded sulphur (0·06 g., 18·7%), and 1 : 2-dihydro-1-methyl-2-thioquinoline (0·36 g.). The same dye was obtained in 15% yield by treating 1-methyl-2-α-phenylphenacylselenoquinolinium bromide with alcoholic triethylamine. This quaternary salt which deposited selenium on attempted purification was formed in 82% yield as an orange powder by refluxing 1 : 2-dihydro-1-methyl-2-selenoquinoline (1·1 g.) and α-phenylphenacyl bromide (1·4 g.) in benzene (10 c.c.) for 5 min. on a steam-bath.

(*f*) 3-*Methyl*-2-α-*phenylphenacylbenzothiazolium bromide*. 3-Methylbenzothiazolin-2-thione (1·8 g.) and desyl bromide (2·75 g.) were fused together for 4 hr. on a steam-bath. The thick oil was dissolved in ethanol (10 c.c.), and triethylamine (1 c.c.) was added. Scratching caused solidification.

3-*Methyl*-2-α-*phenylphenacylbenzothiazoline* (XXX) (1·4 g., 41%) formed lemon-yellow needles, m. p. 203°, on recrystallisation from ethanol then from benzene–light petroleum (b. p. 60—80°) (Found: C, 76·8; H, 4·95; N, 4·3; S, 9·3. $C_{23}H_{17}ONS$ requires C, 77·0; H, 4·95; N, 4·1; S, 9·35%).

Alternative Synthesis of the Disulphide (XXVI).—*Phenacyl thiolbenzoate*. This compound has been obtained by Groth (*Arkiv Kemi, Min., Geol.*, 1924, **9**, 63) by the action of benzoyl chloride on acetophenone-ω-thiol. Preferably it is prepared as follows. Phenacyl bromide (10 g., 0·05 mole), potassium thiolbenzoate (8·9 g., 0·05 mole), and ethanol (20 c.c.) were warmed together for 2 min. on a steam-bath. Potassium bromide separated and was dissolved by the slow addition of water to the warm solution. The required ester commenced to crystallize and was fully precipitated by water (100 c.c.). It was obtained in 92% yield as cream-coloured flakes, m. p. 84—85°, from benzene–light petroleum (b. p. 60—80°) (Found: S, 12·55. Calc. for $C_{15}H_{12}O_2S$: S, 12·5%).

2-α-*Benzoylthiophenacylidene*-3-*methylbenzothiazoline* (XXVII). To 3-methyl-2-methylthiobenzothiazolium toluene-*p*-sulphonate (1·85 g.) and phenacyl thiolbenzoate (1·3 g.) in pyridine (10 c.c.) at 50° triethylamine (0·8 c.c.) was added and the whole was allowed to cool during 3 hr. Ethanol (50 c.c.) was run in slowly with scratching to give yellow crystals. The *product* (0·5 g., 25%) formed lemon-yellow needles in rosettes, m. p. 177°, from ethanol (Found: N, 3·65; S, 15·95. $C_{23}H_{17}O_2NS_2$ requires N, 3·45; S, 15·8%).

Hydrolysis of (XXVII). (*a*) The thiazoline (XXVII) (0·3 g.), ethanol (10 c.c.), and aqueous 4N-sodium hydroxide (0·5 c.c.) were heated for 2 min. on a steam-bath. A red solution resulted from which yellow crystals rapidly separated. The solution was chilled overnight, the red colour of the solution changing to yellow. The crystals, when washed with ethanol, gave the disulphide (XXVI) as yellow flakes, m. p. 262° (from pyridine–ethanol; 0·09 g., 40%) (Found: N, 4·55; S, 21·4), alone or mixed with compound obtained as under (a, ii). The reaction filtrate gave 0·1 g. (50%) of 3-methyl-2-phenacylidenebenzothiazoline (XVI), yellow flakes, m. p. 174—175°, from benzene–light petroleum (b. p. 60—80°).

(*b*) The thiazoline (XXVII) (0·5 g.) in ethanol (60 c.c.) was treated with aqueous 4N-sodium hydroxide (1 c.c.) under a stream of nitrogen. The solution was warmed at 40° for 2 min. and water (50 c.c.) was added. Addition of potassium persulphate (1 g.) in water (15 c.c.) discharged the orange-red colour and precipitated yellow flocks. These were washed with water and ethanol and gave 0·3 g. (80%) of yellow flakes, m. p. 263°, from pyridine–ethanol, identical with previous samples of the disulphide (XXVI).

(*c*) After reaction as described in (*b*) the alkaline solution of the thiol was neutralized with acetic acid, causing immediate discharge of the red colour, the formation of yellow flocks, and a strong odour of hydrogen sulphide (blackened lead acetate wool). The precipitate was washed with ethanol and extracted with boiling ethanol, leaving 0·03 g. (8%) of undissolved disulphide (XXVI), m. p. 262° (from pyridine–ethanol). The ethanol extract on concentration gave 0·2 g. (60%) of 3-methyl-2-phenacylidenebenzothiazoline (XVI), m. p. and mixed m. p. 176° (from ethanol).

The red alkaline solution of the thiol, on addition of ammonia and aqueous silver nitrate, gave an insoluble, orange silver salt.

Reactions of the Disulphide (XXVI).—(*a*) The disulphide (0·5 g.) was treated in pyridine (10 c.c.) with aqueous 2N-sodium hydroxide (10 c.c.) and heated on a steam-bath for 2 hr., the solution, initially orange, becoming almost colourless. Water (10 c.c.) was added, and the solution was concentrated until crystallization occurred. Water (100 c.c.) was added and the yellow flakes were collected. They were air-dried and dissolved in benzene (10 c.c.), and the solution was filtered, concentrated to 5 c.c., and treated with light petroleum (b. p. 60—80°) (25 c.c.). The pale yellow flakes (0·4 g., 90%), m. p. 175—176°, were identical with an authentic specimen of the thiazoline (XVI).

(*b*) The disulphide (XXVI) (0·5 g.) was suspended in benzene (20 c.c.) and a 50% solution of hydrogen bromide in acetic acid (0·5 c.c.) was added, with shaking until the solid had dissolved. The benzene was decanted and acetone (2 c.c.) was added. The yellow crystals (0·55 g., 95%) formed yellow needles, m. p. 203—204°, from ethanol–ether (Found : Br, 22·7; S, 9·05. $C_{16}H_{14}ONBrS$ requires Br, 23·0; S, 9·2%). They are *2-α-hydroxystyryl-3-methylbenzothiazolium bromide* (XVII), identical with a specimen obtained by passing hydrogen bromide into a benzene solution of the ketone (XVI).

(*c*) The disulphide (XXVI) (2·0 g.) was suspended in acetic anhydride (100 c.c.) and saturated with hydrogen bromide. The temperature rose from 22° to 29° and a mass of crystals separated (2·35 g.). From acetic anhydride saturated with hydrogen bromide, then from acetic anhydride, they formed pale yellow needles, m. p. 140° (red) (Found: C, 55·7; H, 4·3; Br, 20·5; S, 7·9. $C_{18}H_{16}O_2NBrS$ requires C, 55·45; H, 4·1; Br, 20·5; S, 8·2%), of *2-α-acetoxystyryl-3-methylbenzothiazolium bromide* (XVIII), identical with specimens obtained by dissolving the enol (XVII) (1 g.) in boiling acetic anhydride (10 c.c.) and chilling it immediately.

The acetic anhydride filtrates were evaporated to dryness to yield 0·095 g. (44·5%) of sulphur (flakes, m. p. 118°, from benzene) and 0·22 g. (12·3%) of ketone (XVI).

The structure of the acetate (XVIII) was determined as follows : (i) The acetate (1·95 g.), 3-allylrhodanine (0·9 g.), ethanol (10 c.c.), and triethylamine (0·8 c.c.) were refluxed for 2 min. The crystals (0·9 g., 42·5%) of *3-allyl-5-[2-(3-methylbenzothiazolin-2-ylidene)-2-phenylethylidene]-2-thiothiazolid-4-one* (XIX) formed green-gold flakes, m. p. 233°, from benzene–ethanol (Found : C, 62·6; H, 4·6; S, 22·9. $C_{22}H_{18}ON_2S_3$ requires C, 62·5; H, 4·25; S, 22·75%). (ii) To the acetate (1·3 g.) suspended in ethanol (20 c.c.) sodium sulphide nonahydrate (1·0 g.) in water (5 c.c.) was added and the whole was heated for 2 min. on the steam-bath. The flocculent red precipitate of 3-methyl-2-thiophenacylidenebenzothiazoline (XX), collected after chilling, formed scarlet needles, m. p. 175° (0·6 g., 63·5%) from benzene–light petroleum (b. p. 60—80°) (Found : S, 22·9. Calc. for $C_{16}H_{13}NS_2$: S, 22·6%). de Smet and Mees (G.P. 740,773) give m. p. 176°.

2-(3-Benzoyl-3-benzoylthioallylidene)-3-ethylbenzothiazoline (XXXIII).—2-2′-Acetanilidovinyl-3-ethylbenzothiazolium iodide (2·25 g.), phenacyl thiolbenzoate (1·3 g.), ethanol (10 c.c.), and triethylamine (0·8 c.c.) were refluxed together on a steam-bath for 10 min. The *dye* separated when the solution was chilled. It (1·25 g., 58%) formed garnet tablets, m. p. 172—173°, from benzene (Found : N, 3·2; S, 14·65. $C_{26}H_{21}O_2NS$ requires N, 3·15; S, 14·45%). Hydrolysis with sodium hydroxide gives an orange, water-soluble product forming an insoluble silver salt. Acidification of the solution of the sodium salt under nitrogen gave orange-red grains which could not be crystallized but readily redissolved in alkali.

2-p-Nitrobenzylthiobenzothiazole.—To potassium hydroxide (5·6 g., 0·1 mole) in ethanol (250 c.c.) 2-mercaptobenzothiazole (16·7 g., 0·1 mole) and *p*-nitrobenzyl chloride (17·15 g., 0·1 mole) were added. The mixture was warmed gently to start the reaction and was then left for 1 hr. and chilled. The solids were filtered off and washed well with ethanol and water. The *sulphide* (28·1 g., 97·5%) formed pale yellow flakes, m. p. 95°, from ethanol (Found : N, 8·9; S, 21·1. $C_{14}H_{10}O_2N_2S_3$ requires N, 9·25; S, 21·2%). It yielded *3-methyl-2-p-nitrobenzylthiobenzothiazolium toluene-p-sulphonate* (XLI) on fusion for 12 hr. on a steam-bath with 1 mol. of methyl toluene-*p*-sulphonate. This (92% yield) formed white crystals, m. p. 209—211° (red melt), decomposing on attempted recrystallization (Found : S, 19·4. $C_{22}H_{20}O_5N_2S_3$ requires S, 19·7%). It (3·9 g.), water (20 c.c.), and triethylamine (1·0 c.c.) were ground together in a boiling-tube and warmed gently until the quaternary salt was converted into a soft black solid. The water was decanted and the residue washed with ethanol. From ethanol containing a little triethylamine the first crop (1·5 g., 66%) formed purple-bronze or red flakes, m. p. 224° after a further recrystallization from benzene–light petroleum (b. p. 80—100°) (Found : C, 63·15; H, 4·3; N, 10·1; S, 11·35. $C_{15}H_{12}O_2N_2S$ requires C, 63·4; H, 4·3; N, 9·85; S, 11·25%). It is *3-methyl-2-p-nitrobenzylidenebenzothiazoline* (XLIII). The second crop (0·3 g., 22·4%) formed pink needles, m. p. 125° [from benzene–light petroleum (b. p. 60—80°)] (Found : C, 50·3; H, 3·8; N, 7·95; S, 18·95. Calc. for $C_{14}H_{12}O_4N_2S_2$: C, 50·0; H, 3·6; N, 8·35; S, 19·05%), of di-(*p*-nitrobenzyl) disulphide, identical with an authentic specimen (Price and Twiss, *J.*, 1908, 1401).

2-p-Nitrobenzylthioquinoline.—This was obtained in 86·5% yield from equimolar quantities of 2-mercaptoquinoline, *p*-nitrobenzyl chloride, and alcoholic potassium hydroxide, as colourless needles, m. p. 87° (from ethanol) (Found : C, 64·7; H, 4·2; N, 9·35; S, 10·95. $C_{16}H_{12}O_2N_2S$ requires C, 64·8; H, 4·05; N, 9·45; S, 10·8%). Its *methotoluene-p-sulphonate*, obtained in 52% yield on a steam-bath (6 hr.), formed flat, buff needles, m. p. 177°, from ethanol–ether

(Found: S, 13·35. $C_{24}H_{22}O_6N_2S_8$ requires S, 13·2%). Its ethanolic solution gave a purple precipitate with triethylamine which resinified on attempted purification.

The author thanks Mr. R. A. Jeffreys and Mrs. M. Weston for the preparation of certain intermediates, also Dr. W. E. Moffitt for stimulating discussions which led to the initiation of this work.

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Compounds containing Sulphur Chromophores. Part II. Attempts to prepare Sulphide Analogues of* mero*Cyanines.*

By E. B. KNOTT and R. A. JEFFREYS

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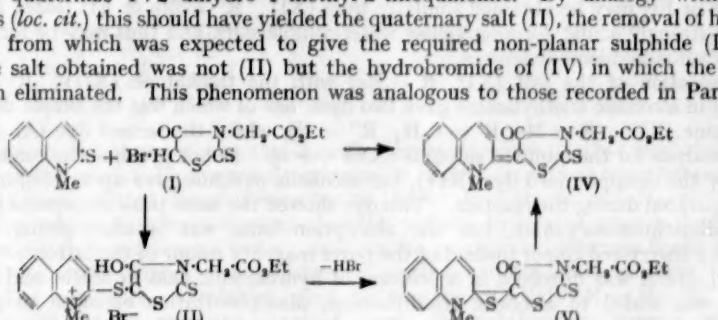
Attempts to prepare sulphides (III, IX, and XV) analogous to *mero*cyanines but in which a sulphur atom is inserted in the bridge between the two end nuclei have given only the *mero*cyanines themselves. The elimination of the sulphur atom from the molecule is analogous to the reaction described in Part I.* In certain cases *mero*cyanine disulphides (XVIII) were isolated.

THE preceding paper was concerned with experiments to obtain compounds containing chromophoric sulphur in which the $+M$ auxochrome was a nitro- or non-cyclic carbonyl group. Concurrent attempts were made to obtain related compounds, analogues of *mero*cyanines, in which the carbonyl auxochrome formed part of a heterocyclic ring.

In the first instance, compounds of type (VII) (Part I*) were sought. 3-Ethoxycarbonylmethylrhodanine was brominated to give the 5-bromo-derivative (I) which was used to quaternize 1 : 2-dihydro-1-methyl-2-thioquinoline. By analogy with similar reactions (*loc. cit.*) this should have yielded the quaternary salt (II), the removal of hydrogen bromide from which was expected to give the required non-planar sulphide (III). In fact, the salt obtained was not (II) but the hydrobromide of (IV) in which the sulphur had been eliminated. This phenomenon was analogous to those recorded in Part I, and



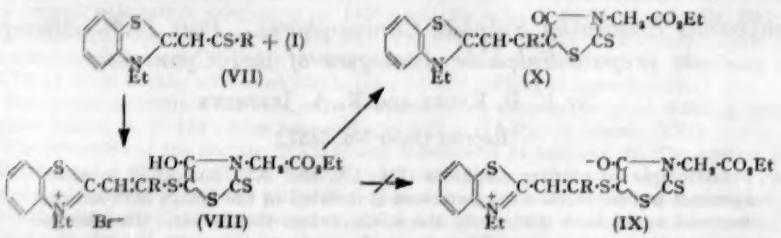
the mechanism based on formation of an intermediate *spiro*episulphide (V) would apply equally.

Similar quaternization of other heterocyclic thiones with (I) proceeded much more slowly or not at all, the fused mixture on treatment with triethylamine giving only the thioindigoid dye (VI). The same dye was also obtained by treating (I) with alcoholic triethylamine. Synthesis of the planar higher vinylogue (IX; R = H) of (II) in the

* Part I, preceding paper.

benzothiazole series was next attempted. 3-Ethyl-2-thioformylmethylenebenzothiazoline (VII; R = H) condensed with the ester (I) to give the red salt (VIII; R = H) smoothly at room temperature. Removal of hydrogen bromide from it gave either a tar or the dimethin*mero*cyanine (X; R = H) with the elimination of sulphur. Similar results were obtained when the starting point was the thioketone (VII; R = Me), the only product being the dye (X; R = Me).

The failure to isolate the salt (II), in view of the ease of formation of the analogous higher vinylogue (VIII), may be a consequence of the steric hindrance to coplanarity of the nuclei of the former salt.



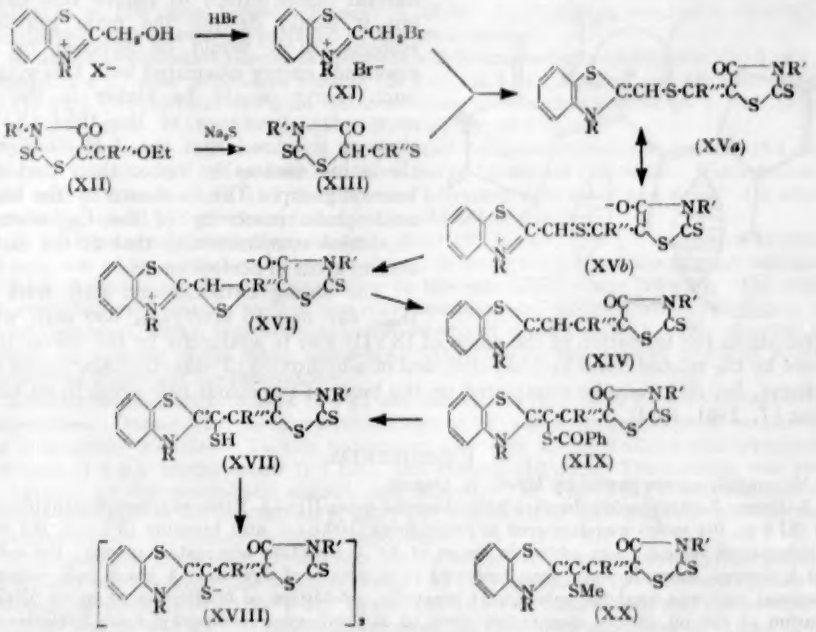
After failure to obtain the required sulphide resonators of type (VII) (*loc. cit.*), attention was turned to the synthesis of their isomers, *i.e.*, of type (VI) (Part I). This required as intermediates a 2-bromomethylbenzothiazole quaternary salt and a 5-thioformylrhodanine. 2-Bromomethylbenzothiazole has been described by Zubarowski (*J. Gen. Chem., U.S.S.R.*, 1951, **21**, 2055), but its quaternary salts (XI) are best obtained by heating the quaternary salts of 2-hydroxymethylbenzothiazole (Anish, U.S.P. 2,508,324; Zubarowski, *loc. cit.*) with 70% aqueous hydrobromic acid. 3-Substituted-5-thioformylrhodanines (XIII; R'' = H) were readily obtained by treating 5-ethoxymethylene-rhodanines (XII; R'' = H) (Knott, *J.*, 1954, 1482) with sodium sulphide. The related thioketones (XIII; R'' = Me or Et) may be obtained similarly from (XII; R'' = Me or Et) (*idem, loc. cit.*). They are strongly acidic, forming yellow water-soluble salts, and thus may be formulated as 5-mercaptoalkylidenerhodanines.

Condensation of the salt (XI; R = Me) with the thioketone (XIII; R' = C_3H_5, R'' = H) in alcoholic triethylamine gave two dyes, one of which was the simple dimethin*mero*cyanine (XIV; R = Me, R' = C_3H_5, R'' = H), whilst the second dye (A) gave the correct analysis for the required sulphide (XV*a* ⟷ *b*). In hot pyridine the condensation gave only the desulphurized dye (XIV), but alcoholic pyridine gave up to 16% of dye A, which separated during the reaction. This dye showed the same peak absorption (520 mμ) as the dimethin*mero*cyanine, but the absorption band was broader, giving the dye solutions a cherry-red colour instead of the purer magenta colour of the latter.

When dye A was dissolved in a solution of hydrobromic acid in acetic acid and the solution was added to alcoholic triethylamine, desulphurization occurred to give the *mero*cyanine (XIV). The red solution of the dye in pyridine–ethanol became an intense blue on addition of aqueous sodium hydroxide, the colour fading to yellow when the solution was heated. The blue solution remained clear on dilution with water, and red flocks were precipitated on acidification. This behaviour is similar to that of the chain hydroxy-dye analogous to the thiol (XVII) (Jeffreys, *J.*, 1954, 503), red solutions of which became blue with alkali or organic bases, the blue colour being attributable to the dye anion. Although its solution did not become blue with organic bases it seemed possible that dye A was the thiol (XVII), which is isomeric with (XV), or the disulphide (XVIII), analogous to the disulphide described in Part I. Such a disulphide would suffer disruption to the thiol anion with alkali hydroxide (cf. Schiller and Otto, *Ber.*, 1876, **9**, 1637; Fromm and Wittmann, *Ber.*, 1908, **41**, 2264). Syntheses of these substances were, therefore, undertaken.

The thiol (XVII) was sought initially by condensation of the quaternary salt of 2-mercaptomethylbenzothiazole and a 5-ethoxymethylenerhodanine (XII; R'' = H).

2-Mercaptomethylbenzothiazole was obtained as an oil by alkaline hydrolysis of benzoylthiomethylbenzothiazole (Part IV, which follows) or by treatment of benzothiazol-2-ylmethylthiuronium bromide with sodium carbonate. It was soluble in alkali and oxidized slowly in air to the disulphide or more readily by persulphate. On gentle treatment of the thiol with methyl sulphate, hydrogen sulphide was evolved and the product, heated with a 5-ethoxymethylenerhodanine in alcoholic triethylamine, gave only the simple dimethin*mero*cyanine (XIV; R″ = H).



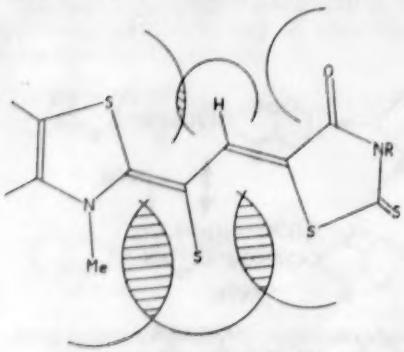
Condensation of 2-benzoylthiomethyl-3-methylbenzothiazolium (methyl sulphate) (Part IV, *loc. cit.*) with 3-allyl-5-ethoxymethylenerhodanine (Knott, *loc. cit.*) at room temperature gave the chain-substituted dimethin*mero*cyanine (XIX; R = Me, R′ = C_3H_5, R″ = H), which on hydrolysis with cold aqueous-alcoholic sodium hydroxide gave a deep blue solution completely miscible with water; acidification precipitated magenta flocks which, when fresh, redissolved readily in pyridine or alcoholic triethylamine to give a blue solution. The substance in solution must be the thiol (XVII; R = Me, R″ = H, R′ = C_3H_5) although it was not obtained pure. Recrystallization gave a product identical with dye A. That this was the disulphide (XVIII; R = Me, R″ = H, R′ = C_3H_5) was shown by oxidizing the blue solution of the thiol salt with persulphate. The blue colour was discharged immediately, and the red flocks proved to be identical with dye A obtained from (XI) and (XIII). The flocks were readily reduced to the thiol salt by sodium sulphide and less rapidly by hydrazine hydrate, the blue solution in the latter case soon fading. Methylation of the blue solution of the thiol salt readily gave the chain methylthio-substituted dye (XX).

The formation of the disulphide (XVIII) from the precursors (XI) and (XIII) occurs rapidly even in the absence of oxygen and, since evolution of the hydrogen sulphide during the reaction was observed, it appears that the formation of the disulphide (XVIII) together with the dimethin*mero*cyanine (XIV) may be caused by the reductive desulphurization of the episulphide (XVI) by the thiol (XVII) (cf. disulphide formation in Part I):

$$2(\text{XVII}) + (\text{XVI}) \longrightarrow (\text{XVIII}) + (\text{XIV}) + H_2S$$

Condensation of the bromide (XI) with the compound (XIII; R″ = Me) gave only one dye, the chain methyl-substituted dimethin*mero*cyanine (XIV; R″ = Me).

It is of interest that the free thiol (XVII) can be isolated, since the related 3-methyl-2-α-mercaptophenacylidenebenzothiazoline (Part I) decomposed immediately on neutralization of the solution of its sodium salt. Both of these compounds suffer from steric hindrance to planarity in that the thiol sulphur atom interferes with the 3-alkyl group (Figure). Episulphide formation would perhaps be a natural isomerization to relieve this strain; but it would destroy the main resonance systems, so it would be opposed by the resonance energy associated with this system. Such energy would be higher in the less asymmetric resonance of the thiol (XVII), since it is known that the $+M$ effect of a rhodanine nucleus is higher than that of a benzoyl group. This is shown by the higher nucleophilic reactivity of the $C_{(5)}$ atom of rhodanine compared with that of the methyl carbon atom of acetophenone.



The strong bathochromic shift from red ($\lambda_{max.}$ 510 mμ) to blue ($\lambda_{max.}$ 650 mμ), which accompanies the formation of the anion of (XVII) and is analogous to the colour shifts shown by the related chain hydroxy-dye, and of α-hydroxy-3:3′-dimethylthiacyanine salts (Jeffreys, *loc. cit.*), may be interpreted on the basis of the colour rule given in an earlier paper (*J.*, 1951, 1024).

Experimental

Microanalyses are partly by Mr. C. B. Dennis.

5-Bromo-3-ethoxycarbonylmethyl-2-thiothiazolid-4-one (I).—3-Ethoxycarbonylmethylrhodanine (21·9 g., 0·1 mole) was dissolved in chloroform (100 c.c.), and bromine (5·2 c.c., 0·1 mole) in chloroform (15 c.c.) was added in drops at 25°. Reaction was instantaneous; the solvent and hydrogen bromide were then removed in a stream of dry air. A thick pale yellow oil remained and was used for subsequent reactions. Addition of triethylamine to an alcoholic solution of the oil gave a quantative yield of *di-(3-ethoxycarbonylmethyl-4-oxo-2-thiothiazolid-5-ylidene)* (VI), brown needles, m. p. 178°, from benzene–ligroin (Found: C, 39·0; H, 3·3; N, 7·1; S, 29·7. $C_{14}H_{14}O_6N_2S_4$ requires C, 38·7; H, 3·2; N, 6·45; S, 29·5%). The same dye was obtained by fusion of equimolar amounts of the bromide (I) with 3-methylbenzothiazol-2-thione on the steam-bath for 1 hr., followed by treatment with alcoholic triethylamine.

3-Ethoxycarbonylmethyl-5-(1:2-dihydro-1-methylquinolin-2-ylidene)-2-thiothiazolid-4-one (IV).—1:2-Dihydro-1-methyl-2-thioquinoline (0·85 g., 0·005 mole) was dissolved in benzene (15 c.c.) and mixed at 25° with a solution of the bromide (I) (1·5 g., 0·005 mole) in benzene (15 c.c.), then heated at 70° for 10 min. to give a cream-coloured solid, m. p. *ca.* 168° (orange melt) with previous softening, after vacuum-drying (Found: C, 42·1; H, 4·05; N, 5·15; Br, 26·95; S, 11·0%). The ratio of N and S to Br indicates that it is a dihydrobromide of (IV), $C_{17}H_{14}O_3N_2S_3.2HBr$, containing some solvent. It was covered with ethanol and an excess of triethylamine was added to give a tar which soon crystallized and formed garnet flakes, m. p. 181°, from benzene–ethanol (Found: S, 18·05. $C_{17}H_{14}O_3N_2S_3$ requires S, 17·9%). It was identical with a specimen of the base (IV) obtained by the condensation of a 1-methyl-2-methylthioquinolinium salt with 3-ethoxycarbonylmethylrhodanine.

2-2′-(3-Ethoxycarbonyl-4-oxo-3-thiothiazolidin-5-ylthio)vinyl-3-ethylbenzothiazolium Bromide (VIII; R = H).—3-Ethyl-2-thioformylmethylenebenzothiazoline (1·1 g., 0·005 mole) in benzene (15 c.c.) was mixed at 23° with a solution of the bromide (I) (1·5 g., 0·005 mole) in benzene (10 c.c.). A red precipitate was formed at once. The mixture was left overnight, and the solid (2·4 g., 92·5%) was collected, washed with benzene, and vacuum-dried. It had m. p. 146°, with softening at 132° (Found: C, 41·9; H, 4·15; N, 5·45; Br, 15·25; S, 24·3. $C_{18}H_{19}O_3N_2BrS_4$ requires C, 41·6; H, 3·7; N, 5·4; Br, 15·4; S, 24·65%). This *salt* (5·2 g.) was covered with chloroform (100 c.c.) and shaken with water (100 c.c.) and sodium hydrogen carbonate (10 g.) for 5 min. The magenta chloroform layer was dried and concentrated to

5 c.c. Benzene (10 c.c.) was added and the flask was chilled. The purple flakes which separated (2·95 g.) formed magenta flakes, m. p. 189°, from benzene (Found: S, 23·85. $C_{18}H_{16}O_3N_2S_3$ requires S, 23·65%), identical with *3-ethoxycarbonylmethyl-5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-thiothiazolid-4-one* (X; R = H).

3-Ethoxycarbonylmethyl-5-[1-(3-ethylbenzothiazolin-2-ylidene)prop-2-ylidene]-2-thiothiazolid-4-one (X; R = Me).—The bromide (I) (3·0 g.) and 3-ethyl-2-thioacetylmethylenebenzothiazoline (VII; R = Me) (Brooker and Keyes, U.S.P. 2,369,647) (2·35 g.) in ethanol (15 c.c.) were heated on the steam-bath for 5 min. The *dye* which crystallized on chilling (1·3 g., 31%) formed magenta needles, m. p. 176°, from benzene (Found: S, 22·65. $C_{19}H_{20}O_3N_2S_3$ requires S, 22·85%). It was identical with a specimen prepared by the usual method.

Benzothiazol-2-ylmethylthiuronium Bromide.—2-Bromomethylbenzothiazole (10·2 g.) and thiourea (3·4 g.) were refluxed in ethanol (50 c.c.) for ½ hr. Cooling and filtration gave the *salt* (13·3 g.). It recrystallized from methanol–ether as colourless needles, m. p. 194° (Found: N, 13·8; Br, 26·2. $C_9H_{10}N_3BrS_2$ requires N, 13·8; Br, 26·3%).

2-Mercaptomethylbenzothiazole.—(*a*) Benzothiazol-2-ylmethylthiuronium bromide (9·1 g.) was dissolved in methanol and poured into an excess of 2N-sodium carbonate. The solution was made acid with acetic acid, and the thiol was extracted with ether and dried. On removal of the ether, an oil (4·5 g.) was obtained. It could not be distilled.

(*b*) To 2-benzoylthiomethylbenzothiazole (Part IV, *loc. cit.*) (5·7 g.), suspended in ethanol (20 c.c.), was added potassium hydroxide (2·5 g.) in water (5 c.c.), and the mixture was shaken for ½ hr., a clear solution being obtained. To this was added water (90 c.c.). The solution was extracted with ether to remove any ethyl benzoate, and acidified with hydrochloric acid. An oil separated, which was extracted with ether and dried (Na_2SO_4). The yield of crude product, on removal of the ether, was 4·6 g. When the oil was allowed to stand, it slowly precipitated crystals of the disulphide.

2-Mercaptomethylbenzothiazole (1·4 g.) and methyl sulphate (0·98 g.) were mixed at room temperature. During 1 hr. the temperature rose to 38° and hydrogen sulphide was evolved. The gum slowly solidified. To this quaternary salt were added 3-allyl-5-ethoxymethylenerhodanine (1·8 g.), triethylamine (1·1 c.c.), and ethanol (15 c.c.). The solution was heated for 10 min. on the steam-bath, chilled, and filtered. The dye (2·2 g.) recrystallized from pyridine–methanol as red needles, m. p. 243°, and was identical with 3-allyl-5-(3-methylbenzothiazolin-2-ylidene-ethylidene)-2-thiothiazolid-4-one (XIV; R = Me, R′ = C_3H_5).

Di(benzothiazol-2-ylmethyl) Disulphide.—A solution of 2-mercaptomethylbenzothiazole (2·8 g.) and sodium hydroxide solution (10%; 20 c.c.) in ethanol (20 c.c.) was shaken with potassium persulphate (5 g.) for ½ hr. Water (50 c.c.) was then added, and the precipitated *disulphide* was filtered off. It recrystallized from benzene–light petroleum as prisms (2·2 g.), m. p. 121° (Found: N, 7·7; S, 35·8. $C_{16}H_{12}N_2S_4$ requires N, 7·8; S, 35·6%).

2-Bromomethyl-3-methylbenzothiazolium Bromide (XI; R = Me).—2-Hydroxymethylbenzothiazole (Zubarowski, *loc. cit.*) (3·3 g.) and methyl toluene-*p*-sulphonate (3·8 g.) were fused together on a steam-bath until solid (15 min.). Aqueous hydrobromic acid (s.g. 1·7) (20 c.c.) was added and the whole heated on a steam-bath for 5 hr., and refluxed for 1 hr. on a gauze. The solvent was then removed under reduced pressure. Acetone (50 c.c.) was added and the crystalline *bromide* collected after chilling. It (5·0 g., 77·5%) formed colourless prisms, m. p. 198° (effervescence), from methanol (Found: Br, 49·1. $C_9H_9NBr_2S$ requires Br, 49·5%). With alcoholic triethylamine a purple colour developed.

2-Bromomethyl-3-ethylbenzothiazolium Bromide (XI; R = Et).—2-Hydroxymethylbenzothiazole (10 g.) and diethyl sulphate (8·0 c.c.) were heated together on a steam-bath for 1 hr. The thick reddish resin crystallized slowly. It was treated with hydrobromic acid (50 c.c.) by the method used for the 3-methyl homologue. The required *bromide* (5·8 g., 28·4%) formed fawn flakes, m. p. 190°, from ethanol (Found: Br, 47·3. $C_{10}H_{11}NBr_2S$ requires Br, 47·5%).

3-Allyl-2-thio-5-thioformylthiazolid-4-one (XIII; R′ = C_3H_5, R″ = H).—3-Allyl-5-ethoxymethylenerhodanine (2·3 g., 0·01 mole), ethanol (10 c.c.), and a solution of sodium sulphide nonahydrate (2·65 g., 0·011 mole) in water (5 c.c.) were shaken mechanically for 15—20 min., or until dissolution was complete. Water (100 c.c.) was added and the orange solution was filtered after 15 min. Addition of 2N-hydrochloric acid (20 c.c.) precipitated an orange oil which on chilling hardened to a friable resin. This *thiazolidone* (2·05 g., 94·5%) could not be crystallized. It was purified by dissolving it in benzene and precipitation with light petroleum (b. p. 60—80°). It was vacuum-dried for analysis (Found: C, 39·35; H, 3·5; N, 6·3; S, 43·6. $C_7H_7ONS_2$ requires C, 38·75; H, 3·2; N, 6·45; S, 44·2%).

3-Allyl-2-thio-5-thioacetylthiazolid-4-one (XIII; R′ = C_3H_5, R″ = Me).—This *compound*

was obtained similarly from 3-allyl-5-1′-ethoxyethylidenerhodanine (Knott, *loc. cit.*) (2·45 g.). The orange oil obtained on acidifying the reaction mixture crystallized rapidly. It (2·15 g., 93%) formed yellow needles, m. p. 58°, from *cyclo*hexane (Found: C, 42·4; H, 4·1; N, 6·0; S, 41·4. $C_8H_9ONS_3$ requires C, 41·9; H, 3·9; N, 6·05; S, 41·5%).

Di-[1-(3-*methylbenzothiazolin*-2-*ylidene*)-2-(3-*allyl*-4-*oxo*-2-*thiothiazolid*-5-*ylidene*)*ethyl*] *Disulphide* (XVIII; R = Me, R′ = C_3H_5, R″ = H).—(*a*) Solutions of 2-bromomethyl-3-methylbenzothiazolium bromide (3·23 g., 0·01 mole) in methanol (30 c.c.) and of 3-allyl-5-thioformylrhodanine (2·17 g., 0·01 mole) in methanol (20 c.c.) and triethylamine (3·0 c.c., 0·02 mole) were mixed at room temperature. A red tar which was formed immediately soon solidified. It was collected and washed with methanol and the filtrates were kept. From benzene (250 c.c.) followed by pyridine–ethanol the *disulphide* formed green flakes, m. p. 253°, in 10·4% yield (0·4 g.) (Found: C, 51·25; H, 3·55; N, 7·4; S, 33·85. $C_{22}H_{24}O_2N_4S_8$ requires C, 50·95; H, 3·45; N, 7·45; S, 34·0%), $\lambda_{max.}$ 520 mμ in pyridine. The original filtrate and the benzene filtrate on concentration yielded 0·4 g. (11·6%) of 3-*allyl*-5-(3-*methylbenzothiazolin*-2-*ylidene*-*ethylidene*)-2-*thiothiazolid*-4-*one* (XIV; R = Me, R′ = C_3H_5, R″ = H) as flat, dark red needles, m. p. 243°, from pyridine–ethanol (Found: S, 28·05. $C_{16}H_{14}ON_2S_3$ requires S, 27·75%). It was identical with a sample prepared by the conventional method.

(*b*) By heating the above quaternary salt and rhodanine (as in *a*) for 3 min. on a steam-bath in a mixture of pyridine (5 c.c.) and ethanol (25 c.c.) the dye, m. p. 253°, which crystallized during that time, was obtained in 16% yield.

(*c*) 2-Benzoylthiomethyl-3-methylbenzothiazolium (methyl sulphate) (Part IV) (4·1 g.), 3-allyl-5-ethoxymethylenerhodanine (2·3 g.), pyridine (25 c.c.), and triethylamine (1·5 c.c.) were dissolved with shaking and kept for 3 hr. at 25°. Ethanol (50 c.c.) was added and the solution was seeded. 3-*Allyl*-5-[2-*benzoylthio*-2-(3-*methylbenzothiazolin*-2-*ylidene*)*ethylidene*]-2-*thiothiazolid*-4-*one* (XIX; R = Me, R′ = C_3H_5, R″ = H) separated; after 3 hr. a further 150 c.c. of ethanol were added, and the solution was chilled overnight. The dye (2·3 g., 47·5%) formed red flakes with a gold reflex, m. p. 207°, from benzene (Found: N, 6·05; S, 26·95. $C_{23}H_{18}O_2N_2S_4$ requires N, 5·8; S, 26·55%).

It (0·5 g.) was dissolved in hot pyridine (10 c.c.), cooled to 30°, and mixed with sodium sulphide monohydrate (1·0 g.) or sodium hydroxide (0·5 g.) in water (2 c.c.) and ethanol (10 c.c.). Hydrolysis was instantaneous as indicated by the appearance of a brilliant blue colour. Water (40 c.c.) was added to give a clear blue solution.

Addition of potassium persulphate (2·0 g.) in water (20 c.c.) resulted in discharge of the blue colour and precipitation of red flocks. They formed green flakes (0·355 g., 91%), m. p. 253°, from pyridine–ethanol, identical with the product (XVIII; R = Me, R′ = C_3H_5, R″ = H) obtained by the reactions (*a*) or (*b*). Oxidation with hypochlorite gave only a 20% yield of the same dye.

When the solution obtained by hydrolysis was acidified with acetic acid in an atmosphere of carbon dioxide it gave red flocks which were soluble in alcoholic triethylamine or in pyridine to give a deep blue solution. Recrystallization from pyridine–ethanol with access of air gave 0·385 g. (99%) of green flakes, m. p. 252°, identical with the disulphide obtained by the reaction (*a*), (*b*), or (*c*).

3-*Allyl*-5-[2-(3-*methylbenzothiazolin*-2-*ylidene*)-2-*methylthioethylidene*]-2-*thiothiazolid*-4-*one* (XX; R = Me, R′ = C_3H_5, R″ = H).—To the blue solution formed by the hydrolysis of (XIX; R = Me, R′ = C_3H_5, R″ = H), prepared as above, aqueous 2N-sodium hydroxide (10 c.c.) was added, and methyl sulphate (1 c.c.) was allowed to drip in at room temperature with shaking. The blue colour disappeared and red flakes of the *methyl sulphide* separated. They (0·45 g., 86·5%) formed flat magenta needles, m. p. 207°, from benzene–ethanol (Found: N, 7·35; S, 32·7. $C_{17}H_{16}ON_2S_4$ requires N, 7·45; S, 32·7%).

Di-[1-(3-*ethylbenzothiazolin*-2-*ylidene*)-2-(3-*allyl*-4-*oxo*-2-*thiothiazolid*-5-*ylidene*)*ethyl*] *Disulphide* (XVIII; R = Et, R′ = C_3H_5, R″ = H).—2-Bromomethyl-3-ethylbenzothiazolium bromide (3·4 g.) was dissolved in cold methanol (15 c.c.) and added to a solution of 3-allyl-5-thioformylrhodanine (2·2 g.) in methanol (10 c.c.) containing triethylamine (3 c.c.). A red tar was precipitated immediately. This *disulphide* (0·85 g.) recrystallized from benzene as green-red flakes (0·3 g., 7·65%), m. p. 241°, from pyridine–ethanol (Found: C, 52·15; H, 4·15; N, 6·9; S, 32·4. $C_{24}H_{30}O_2N_4S_8$ requires C, 52·15; H, 3·8; N, 7·15; S, 32·7%). The original filtrate and the benzene filtrate on concentration gave 0·65 g. (18·0%) of dark red needles, m. p. 225°, from pyridine–ethanol (Found: S, 26·9. $C_{17}H_{16}ON_2S_3$ requires S, 26·7%), identical with 3-*allyl*-5-(3-*ethylbenzothiazolin*-2-*ylidene*-*ethylidene*)-2-*thiothiazolid*-4-*one* (XIV; R = Et, R′ = C_3H_5, R″ = H) prepared by normal methods.

Action of Hydrogen Bromide on the Disulphide (XVIII; R = Me, R′ = C_2H_5, R″ = H).—The disulphide (0·2 g.) was covered with benzene (20 c.c.), and a 40% solution of hydrogen bromide in acetic acid (5 c.c.) was stirred in until the dye had dissolved to a yellow solution. The benzene was decanted after 5 min. and the solution poured into a solution of triethylamine (10 c.c.) in ethanol (25 c.c.). Addition of water (50 c.c.) to the bright red solution precipitated a dye (0·12 g.) which, after recrystallization from benzene (twice) followed by pyridine–ethanol, formed flat red needles (0·06 g., 33%), m. p. 242°, identical with the *mero*cyanine (XIV; R = Me, R′ = C_2H_5, R″ = H) (Found: N, 8·3; S, 27·8%).

RESEARCH LABORATORIES, KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX.

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Compounds containing Sulphur Chromophores. Part III. Experiments on the Synthesis of Ionic Dyes.*

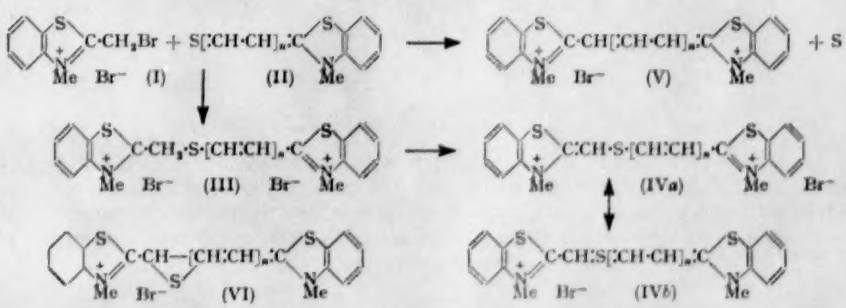
By EDWARD B. KNOTT.

[Reprint Order No. 5458.]

Reactions which were designed to give molecules related to cyanines and oxonols but carrying a sulphur atom in the conjugated chain between the end nuclei have led only to the parent cyanines and oxonols.

IN Parts I and II* it has been shown that reactions which should lead to non-ionic compounds containing a sulphur atom in the conjugation path of a resonator usually give desulphurized products. The present paper is concerned with attempts to obtain cationic and anionic sulphides designed to show whether the sulphur atom is capable of functioning as a chromophore.

Cationic Dyes.—Synthesis of the sulphide (IV*a* ⟷ *b*; $n = 0$) was sought by quaternization of 3-methylbenzothiazolin-2-thione (II; $n = 0$) with 2-bromomethyl-3-methylbenzothiazolium bromide (I), followed by removal of hydrogen bromide from the bisquaternary salt (III). Reaction in boiling methanol gave the yellow 3 : 3′-dimethylthiacyanine bromide (V; $n = 0$) (66·5% yield), the iodide from which was identical with a specimen obtained according to Mills's procedure (*J.*, 1922, 455), together with elementary sulphur and a small amount of blue dye which, however, was not (IV; $n = 0$). Similar

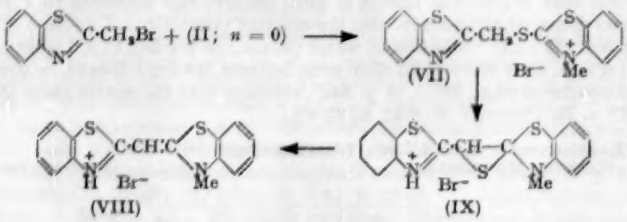


attempts to obtain the dye (IV; $n = 1$) from the precursor (II; $n = 1$) gave only thiacarbocyanine (V; $n = 1$). The elimination of sulphur already encountered in Parts I and II is thus repeated, and it can be assumed once more that the episulphide (VI) is an intermediate.

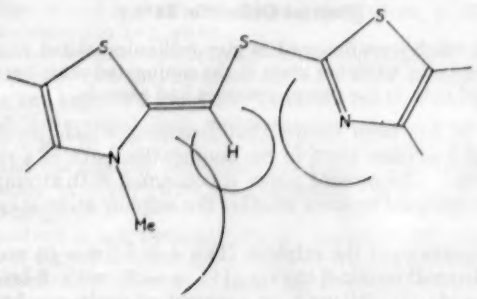
As this direct method failed, two-stage syntheses by two routes were examined. Condensation of 2-bromomethylbenzothiazole with (II; $n = 0$) was intended to give the monoquaternary salt (VII) and thence the dimethobromide (III; $n = 0$). However, it gave

* Parts I and II, preceding papers.

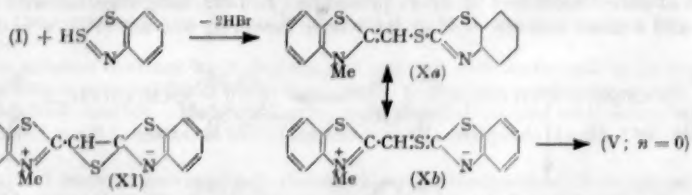
the hydrobromide (VIII) of the cyanine base (cf. Hamer, *J.*, 1940, 7991), probably by way of the episulphide (IX) similar to (VI).



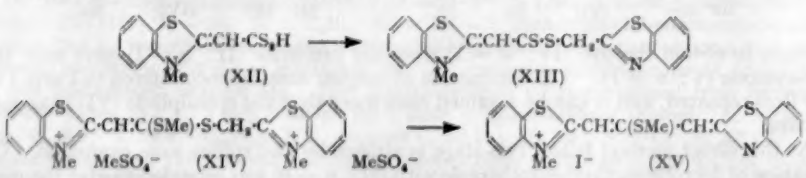
2-Bromomethyl-3-methylbenzothiazolium bromide (I) was made to react with 2-mercaptobenzothiazole in the presence of a base to give the required planar sulphide (X) (see Figure), analogous to a cyanine base and perhaps capable of the resonance (X*a* ⟷ *b*); its notable stability is discussed in Part IV (following paper) together with that of the



hypothetical episulphide (XI). Quaternization with methyl iodide or methyl sulphate again resulted in desulphurization and formation of the thiacyanine (V; $n = 0$).

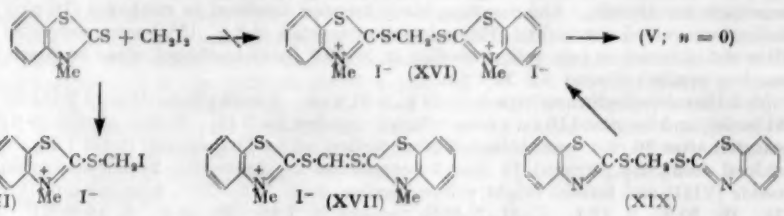


Similarly, condensation of 2-dithiocarboxymethylene-3-methylbenzothiazoline (XII) (Kendall and Majer, B.P. 549,201) which with 2-bromomethylbenzothiazole gave the ester (XIII), with methyl sulphate gave a yellow tar, presumably the required diquaternary salt (XIV) since on its treatment with triethylamine the chain-substituted carbocyanine (XV) (cf. Fry, B.P. 678,626) was the only product isolated.



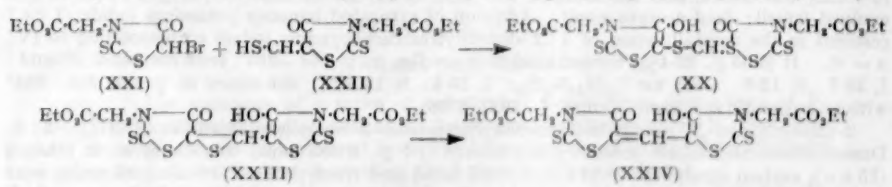
The introduction of two sulphur atoms into the chain of a polymethin dye could give a symmetrical molecule, and the synthesis of (XVII), which is planar, was attempted. The

required intermediate was the diquaternary salt (XVI), from which it was hoped to remove hydrogen iodide to give (XVII). 3-Methylbenzothiazol-2-thione and methylene iodide at 95—100° gave only 2-iodomethylthio-3-methylbenzothiazolium iodide (XVIII) whilst at higher temperatures decomposition with evolution of methanedithiol (?) set in. 2-Mercaptobenzothiazole, however, gave the base (XIX) and thence a diquaternary compound (cf. XVI), isolated as the iodide or perchlorate. Treatment of the di-iodide (XVI) with a variety of bases failed, however, to give the compound (XVII) or indeed any significant colour change. Prolonged heating with alcoholic triethylamine gave traces of thiacyanine (V; $n = 0$) with slow evolution of hydrogen sulphide.



This unexpected stability of the salt (XVI) towards bases indicated the lack of acidity of the methylene group, the chain-sulphur atoms being unable to transmit the $+M$ effects of the quaternary nitrogen atoms sufficiently strongly to cause hyperconjugation of the methylene hydrogen atoms.

Anionic Dyes.—An attempt was next made to obtain the oxonol-type sulphide (XX). However, the 5-bromo-rhodanine (XXI) and the mercaptomethylene derivative (XXII) in



the presence of triethylamine gave the triethylamine salt of di-(3-ethoxycarbonylmethyl 2-thio-5-thiazolid-4-one)methinoxonol (XXIV). The loss of sulphur from the presumed intermediate (XX) may also proceed through the intermediate episulphide (XXIII).

Experimental

Microanalyses are partly by Mr. C. B. Dennis.

Attempts to prepare the Sulphide (IV; $n = 0$).—(*a*) 2-Bromomethyl-3-methylbenzothiazolium bromide (1·6 g., 0·005 mole), 3-methylbenzothiazol-2-thione (0·9 g., 0·005 mole), and methanol (10 c.c.) were heated together for 2—3 min. on a steam-bath until a clear, deep yellow-green solution was obtained. The crystals (1·0 g.) which separated on chilling, together with a further crop (0·3 g.) obtained on concentration of the filtrate, formed canary-yellow needles (1·05 g., 53·5%), m. p. 292—293°, from methanol (Found: N, 7·1; Br, 19·9; S, 16·2. Calc. for $C_{17}H_{15}N_2BrS_2$: N, 7·35; Br, 20·45; S, 16·4%), identical with 3:3′-dimethylthiacyanine bromide obtained by Hamer's method (*J.*, 1930, 2522; m. p. 287°). The iodide formed yellow needles, m. p. 292°, from methanol (Found: I, 29·3; S, 14·8. Calc. for $C_{17}H_{15}N_2IS_2$: I, 29·0; S, 14·6%); Fisher and Hamer (*loc. cit.*) give m. p. 290—292°. The filtrate on concentration gave yellow crystals and a purple tar. A little cold ethanol was added to dissolve the tar and the crystals were collected. They formed flat needles (0·02 g.), m. p. 118°, from benzene–ethanol (Found: S, 99·7%). Addition of aqueous potassium iodide to the solution of the purple tar gave green crystals (0·05 g.) which after recrystallisation from methanol (blue solution) had m. p. 238° (Found: N, 6·0; I, 34·8; S, 13·0%).

(*b*) 2-Bromomethyl-3-methylbenzothiazolium bromide (3·25 g., 0·01 mole) in hot methanol (25 c.c.) was treated with a solution of 2-mercaptobenzothiazole (1·7 g., 0·01 mole) and potassium

hydroxide (0·56 g., 0·01 mole) in methanol (15 c.c.). The mixture became cloudy, and addition of triethylamine (1·5 c.c., 0·01 mol.) after 1 min. caused separation of a granular precipitate, which was collected after 30 min. and washed with methanol, water, and methanol. 2-(*Benzothiazol-2-ylthiomethylene*)-3-*methylbenzothiazoline* (X) (2·4 g., 73%) was obtained as fawn leaflets, m. p. 197°, from pyridine–ethanol (Found: C, 58·4; H, 4·05; N, 8·6; S, 29·1. $C_{16}H_{12}N_2S_3$ requires C, 58·55; H, 3·65; N, 8·55; S, 29·3%).

(i) This product (X) (1·0 g.) and methyl iodide (10 c.c.) were refluxed for 2 hr., giving black flocks, forming rust-coloured needles from methanol in 8% yield (Found: S, 14·4), m. p. 292°, or 293° when mixed with the iodide of the dye (IV; $n = 0$).

(ii) The intermediate (X) (1·0 g.) and methyl sulphate (0·3 c.c.) were heated together on a steam-bath for 15 min. The resulting black tar was dissolved in methanol (10 c.c.) and the solution was chilled overnight. The pale yellow crystals (0·2 g., 15%) were converted into the iodide and obtained as pale yellow needles, m. p. 292° (from methanol) alone or mixed with the preceding product (Found: S, 14·7%).

(*c*) 2-Bromomethylbenzothiazole (2·28 g., 0·01 mole), 3-methylbenzothiazol-2-thione (1·81 g., 0·01 mole), and benzene (10 c.c.) were refluxed together for 2 hr. Yellow needles (0·6 g.) which separated after 30 min. were collected after chilling and a further crop (total 1·5 g., 40%) was obtained from the filtrate. It was *2-benzothiazol-2′-ylmethylene-3-methylbenzothiazolinium bromide* (VIII) and formed bright yellow needles, m. p. 256—257°, from ethanol (Found: N, 7·35; Br, 20·9; S, 17·1. $C_{16}H_{13}N_2BrS_2$ requires N, 7·45; Br, 21·2; S, 16·95%). The base formed orange-yellow needles, m. p. 172° (from ethanol) (Found: N, 9·45; S, 21·8. Calc. for $C_{16}H_{12}N_2S_2$: N, 9·45; S, 21·65%) alone or mixed with Dr. Hamer's specimen (*J.*, 1940, 799; m. p. 176°); Mills (*J.*, 1922, 455) reports m. p. 172°.

Attempt to prepare the Sulphide (IV; $n = 1$).—2-Bromomethyl-3-methylbenzothiazolium bromide (1·7 g.), 3-methyl-2-thioformylmethylenebenzothiazoline (1·1 g.), and methanol (10 c.c.) were heated together for 1 min. on a steam-bath, and then cooled to 20°. Triethylamine (0·8 c.c.) was added, and the solution was kept at 20° for 30 min. Hydrogen sulphide was evolved (smell; lead acetate wool). Addition of saturated aqueous potassium iodide (1 c.c.) resulted in the crystallization of 3:3′-dimethylthiacarbocyanine iodide corresponding to (V; $n = 0$). It (0·55 g., 22·4%) formed steel-blue needles, m. p. 264—265°, from methanol (Found: I, 25·7; S, 12·8. Calc. for $C_{21}H_{21}N_2IS_3$: I, 25·8; S, 13·0%); the mixed m. p. was 264—264° with an authentic specimen (Hamer, *J.*, 1927, 2796).

2-(*Benzothiazol-2′-ylmethyldithiocarbonylmethylene*)-3-*methylbenzothiazoline* (XIII).—2:3-Dimethylbenzothiazolium toluene-*p*-sulphonate (1·7 g., 0·005 mole) was dissolved in ethanol (15 c.c.), carbon disulphide (0·33 c.c., 0·0055 mole) and triethylamine (1·5 c.c., 0·1 mole) were added, and the deep orange solution was refluxed for 10 min. A solution of 2-bromomethylbenzothiazole (1·15 g., 0·005 mole) in ethanol (10 c.c.) was then added with vigorous shaking and the required *ester* separated at once as a thick, yellow meal. It was washed with ethanol and obtained as yellow threads (1·7 g., 87%), m. p. 239°, from pyridine–ethanol (Found: N, 7·1; S, 33·3. $C_{18}H_{14}N_2S_4$ requires N, 7·25; S, 33·2%).

Di-(3-*methyl-2-benzothiazole*)-β-*methylthiotrimethincyanine Iodide* (XV).—The ester (XIII) (1·25 g.) and methyl sulphate (2 c.c.) were fused together on a steam-bath for 30 min. The orange-red melt was dissolved in cold ethanol (20 c.c.), filtered from a small insoluble residue, and treated with triethylamine (2 c.c.). The dye (0·65 g., 42%) which crystallized was converted into the *iodide*, magenta threads, m. p. 252° (from methanol) alone or mixed with a specimen prepared by Fry's method (*loc. cit.*) (Found: N, 5·25; I, 25·1; S, 19·65. $C_{20}H_{19}N_2IS_3$ requires N, 5·5; S, 24·9; S, 18·85%).

2-*Iodomethylthio*-3-*methylbenzothiazolium Iodide* (XVIII).—3-Methylbenzothiazol-2-thione (7·2 g., 0·04 mole) and methylene iodide (1·6 c.c., 0·02 mole) were fused together on a steam-bath for 5 hr. The crystalline cake was washed with warm ethanol to remove unchanged thione and the quaternary *salt* (78% yield) obtained as yellow needles, m. p. 190—193° (decomp.), from methanol (Found: I, 56·8; S, 14·6. $C_9H_9NI_2S_2$ requires I, 56·5; S, 14·25%).

Di(*benzothiazol-2-ylthio*)*methane* (XIX).—Potassium hydroxide (11·2 g., 0·2 mole) was dissolved in ethanol (200 c.c.), 2-mercaptobenzothiazole (36·7 g., 0·22 mole) and methylene iodide (8·1 c.c.; 0·1 mole) were added, and the whole was refluxed for 1 hr. Water (500 c.c.) was added to precipitate a yellow oil which crystallized rapidly. This *compound* (XIX) (30·8 g., 89%) formed pale yellow crystals, m. p. 75°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 8·3; S, 37·3. $C_{15}H_{10}N_2S_4$ requires N, 8·1; S, 37·0%). The base (XIX) (1·75 g.) and methyl iodide (10 c.c.) were refluxed on a steam-bath for 48 hr. The precipitated *dimethiodide* was washed with acetone and obtained in 9·6% yield (0·3 g.) as buff needles, m. p. 153°

(effervescence), from methanol–ether (Found: N, 4·35; I, 39·95; S, 20·35. $C_{17}H_{16}O_2I_2S_4$ requires N, 4·45; I, 40·3; S, 20·3%). The *dimethoperchlorate* was obtained in 59% yield by fusing the base (1·75 g.) and methyl sulphate (1 c.c.) for 5 min. on a steam-bath, dissolving the melt in ethanol (20 c.c.), and adding saturated aqueous sodium perchlorate (0·5 c.c.). The resulting yellow tar was boiled with ethanol (20 c.c.) until it solidified and was then obtained as orange needles, m. p. 176—178°, from methanol (Found: N, 4·95; Cl, 12·15; S, 22·4. $C_{17}H_{16}O_8N_2Cl_2S_4$ requires N, 4·85; Cl, 12·35; S, 22·3%).

When the base (3·5 g.) and methyl sulphate (2 c.c.) were fused as above and the quaternary salt was refluxed in ethanol (10 c.c.) and triethylamine (1·5 c.c.) for 2 hr., hydrogen sulphide was evolved and addition of aqueous potassium iodide gave 0·05 g. of 3 : 3′-dimethylthiacyanine iodide (V; $n = 0$), m. p. and mixed m. p. 292° (from methanol) (Found: I, 28·7; S, 14·9%).

Attempt to obtain the Sulphide (XX).—5-Bromo-3-ethoxycarbonylmethylrhodanine (preceding paper) (1·5 g.) and 3-ethoxycarbonylmethyl-5-thioformylrhodanine (1·3 g.) were dissolved in ethanol (20 c.c.), then cooled to 20°, and triethylamine (1·5 c.c.) was added. Crystals of di-(3-ethoxycarbonylmethyl-4-oxo-2-thiothiazolid-4-ylidene) (VI of previous paper) separated rapidly. After chilling overnight the solution was filtered and the filtrate diluted with ether (100 c.c.). The precipitated tar gradually hardened. It was washed with ether, redissolved in ethanol (10 c.c.), and precipitated by slow addition of ether (50 c.c.). The green deliquescent crystals had no definite m. p. (Found: N, 8·05; S, 23·6. $C_{21}H_{21}O_6N_3S_4$ requires N, 7·9; S, 24·0%). $\lambda_{max.}$ 537 mμ (in methanolic triethylamine).

RESEARCH LABORATORIES, KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX.

[*Received, June 11th*, 1954.]

Compounds containing Sulphur Chromophores. Part IV. Derivatives of Heterocyclic Methylene Bases.*

By EDWARD B. KNOTT.

[Reprint Order No. 5459.]

The synthesis of a series of substituted 2-methylene derivatives of 3-methylbenzothiazoline and of 1 : 2-dihydro-1-methylquinoline is described. Sulphur is readily removed from the 2-benzoylthiomethylene derivatives in alcoholic triethylamine, yielding the 2-phenacylidene analogues.

The stabilities of such sulphides in which a $+M$ and a $-M$ group are linked by a sulphur atom are compared with those of related compounds and are correlated with structures.

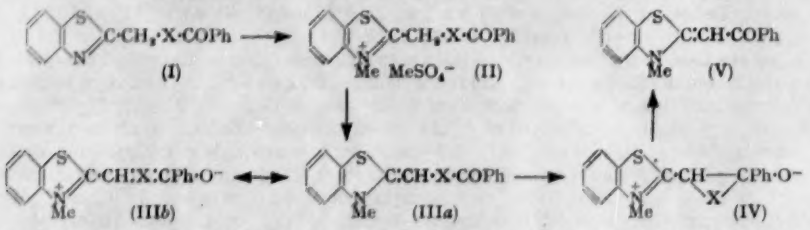
The absorption spectra of these compounds provide evidence that a sulphur atom may utilize its *d*-orbitals and function as a resonance transmitter, although it is not equivalent to a vinylene group. An oxygen atom may behave in the same way.

PRECEDING Parts * recorded unsuccessful attempts to synthesise compounds designed to show whether sulphur could function as a chromophoric atom, *i.e.*, a resonance transmitter. The present paper describes the synthesis of non-ionic sulphides (of type VI in Part I), derivatives of heterocyclic methylene bases, and related compounds required for comparison of absorptions.

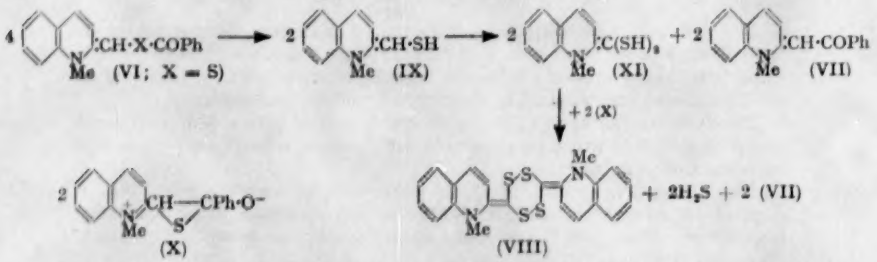
First, when it was believed that the sulphide (XV, of Part I) had been obtained it was of interest to prepare its isomer (III; X = S) in which the ·S·CH: group was replaced by :CH·S·. Condensation of 2-bromomethylbenzothiazole with potassium thiolbenzoate gave 2-benzoylthiomethylbenzothiazole (I; X = S). Removal of methyl hydrogen sulphate from the salt (II; X = S) at room temperature by triethylamine yielded the bright yellow 2-benzoylthiomethylene-3-methylbenzothiazoline, which, if the octet of the chain-sulphur atom expands, may be represented by the hybrid (III$a \longleftrightarrow b$; X = S). The yellow colour of its solutions is discharged by mineralacid but not by acetic acid. This compound decomposes to a pale yellow tar with the evolution of hydrogen sulphide at

* Parts I—III, preceding papers.

20—25° during 7 days, and in boiling alcoholic triethylamine rapidly gives 3-methyl-2-phenacylidenebenzothiazoline (V), in 80% yield, and a bright orange solid of high sulphur content. As suggested in earlier parts, intermediate formation of the episulphide (IV; X = S) is a possible step in the decomposition.



Similar reactions gave the orange-coloured 2-benzoylthiomethylene-1 : 2-dihydro-1-methylquinoline (VI; X = S), which was also decomposed by alcoholic triethylamine to give 1 : 2-dihydro-1-methyl-2-phenacylidenequinoline (VII), in 53% yield, and a compound $(C_{11}H_9NS_2)_x$. The latter is very insoluble and its molecular weight has not been determined. It is insoluble in alkali and cannot, therefore, be the dithiol (XI). It is only the second compound (see Part I), isolated from such a desulphurization, which has been formed by the reaction of the starting material, or of a reaction product, with the sulphur liberated in the main reaction. This compound is probably (VIII), its stability ruling out a linear tetrasulphide structure. It may be formed by addition of sulphur to the hydrolysis product (IX) [from (VI; X = S)] by way of the episulphide (X) to give the dithiol (XI), followed by the oxidation of the last by more episulphide to give (VIII) and hydrogen sulphide. Such oxidation resulting in disulphide formation in the absence of atmospheric oxygen has been recorded in Parts I and II. Alternatively the thiol (IX) may have been oxidized to its disulphide before addition of sulphur occurred.



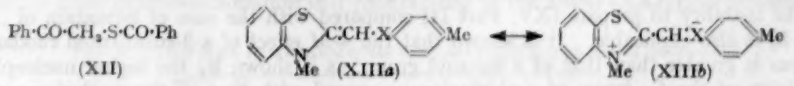
For comparison of absorptions the compounds related to (III; X = S) in which the chain-sulphur atom was replaced by an oxygen atom or a vinylene group were required. 2-Benzoyloxymethylbenzothiazole (Zubarowski, *J. Gen. Chem. U.S.S.R.*, 1951, **21**, 2055) gave the methyl sulphate (II; X = O), and thence an oil, presumably (III; X = O), on treatment with a base. The oil, which could not be distilled without decomposition, did not give the ketone (V) with boiling alcoholic triethylamine. This difference between the behaviour of (III; X = S) and (III; X = O) may indicate a greater resistance of the latter to formation of the epoxide (IV; X = O) or a higher stability of the hypothetical epoxide. Alternatively it may indicate that the expansion of the sulphur electron octet is instrumental in episulphide formation by a form of " short circuit " mechanism which may be depicted as (III*b*; X = S) ⟶ (IV; X = S).

A very dilute alcoholic solution of 2-benzoyloxymethyl-1-methylquinolinium (methyl sulphate) (obtained from 2-bromomethylquinoline) with triethylamine gave a strong yellow colour believed to be due to the liberation of the base (VI; X = O). In more concentrated solution this initial colour faded rapidly as a pink solid was precipitated. The latter darkened in light and was converted into a purple dye on fusion or when heated with

alcoholic triethylamine. It gave the correct analysis for (VI; X = O), but its high melting point, lack of colour, and low solubility in organic solvents are more consistent with its being the isomeric, mesoionic epoxide analogous to (X).

Condensation of 2 : 3-dimethylbenzothiazolium toluene-*p*-sulphonate with sodium hydroxymethyleneacetophenone gave 2-3′-benzoylallylidene-3-methylbenzothiazoline (III; X = ·CH:CH·), but the quinoline analogue could not be isolated in a pure form.

For comparison of the absorption of (III; X = S) with that of compounds containing the same fragments on either side of the chain-sulphur atom, phenacyl thiolbenzoate (XII)



(XII) (XIII*a*) (XIII*b*)

and 3-methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII*a*; X = S) were prepared. The latter was obtained by the condensation of 2-bromomethylbenzothiazole with *p*-thiocresol to give 2-*p*-tolylthiomethylbenzothiazole which was quaternized and then treated with triethylamine. For further spectrographic comparisons 3-methyl-2-*p*-tolyloxymethylenebenzothiazoline (XIII*a*; X = O) was obtained as a light-sensitive powder by reactions analogous to those employed for preparation of (XIII*a*; X = S).

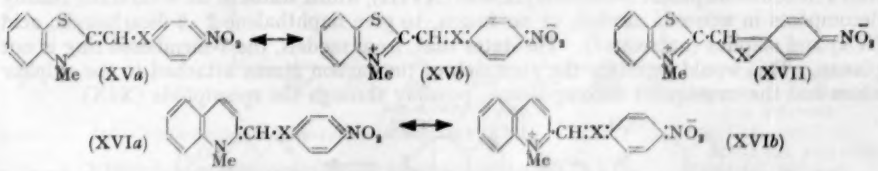
The 1 : 2-dihydroquinoline analogues (XIV*a*; X = S or O) were prepared similarly.

The second type of sulphide required is represented by 3-methyl-2-*p*-nitrophenylthiomethylenebenzothiazoline (XV*a*; X = S), the synthesis of its isomer (XLII of Part I)

(XIV*a*) (XIV*b*)

having proved unsuccessful. By a procedure analogous to that used for (XIII*a*) the required sulphide was obtained as stable, orange crystals.

The related 1 : 2-dihydro-1-methyl-2-*p*-nitrophenylthiomethylenequinoline (XVI*a*; X = S) was obtained similarly, as were also the analogous 2-*p*-nitrophenoxy-analogues (XV*a*, XVI*a*; X = O).



(XV*a*) (XV*b*) (XVII)

(XVI*a*) (XVI*b*)

There is considerable evidence (for references see Part I; also Koch and Moffitt, *Trans. Faraday Soc.*, 1951, **47**, 7; Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058) that a sulphone sulphur atom may expand its electron octet and function as a $+M$ rather than a $+I$ group. A variation of the present type of methylene base was therefore synthesized in order to substantiate this evidence. 2-Bromomethylquinoline and sodium toluene-*p*-sulphinate gave 2-*p*-tolylsulphonylmethylquinoline, which was treated with methyl sulphate. The resulting salt with triethylamine yielded the yellow 1 : 2-dihydro-1-methyl-2-*p*-tolylsulphonylmethylenequinoline (XIV; X = SO_2). The benzothiazoline analogue (XIII; X = SO_2) was obtained similarly. Both these compounds appear, from models, to be planar.

The Stabilities of the Above Sulphides and Those of Parts I, II, *and* III.—In most cases it has been shown that the instability of these sulphides is associated with the loss of the chain sulphur-atom and the formation of an unsaturated resonator. If episulphide formation is a necessary step in this decomposition, then the greater the energy difference between any sulphide and its episulphide the more stable will the sulphide be.

If the isomeric pairs (III; X = S) and (XV of Part I) are first considered, then the isomerization of the former to give the mesoionic (IV; X = S) requires the energy of

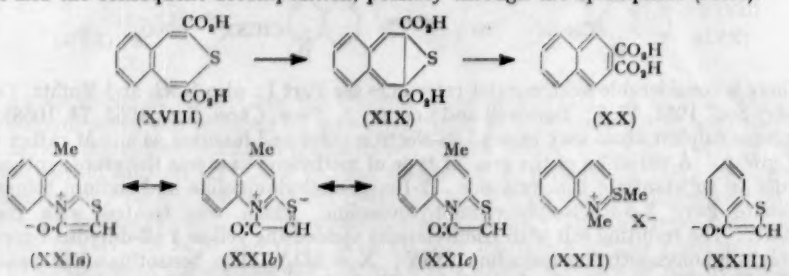
charge separation. A similar change in (XV, Part I) to give (XXXI, Part I), however, involves charge neutralization to give a non-ionic molecule. The actual higher stability of (III; X = S) over (XV of Part I) would therefore be expected.

Similarly, whereas the isomerization of (XV; X = S) to (XVII; X = S) requires the energy of charge separation and results in the loss of Kekulé resonance in the phenylene group the similar isomerization of its isomer (XLII, Part I) to (XLIV, Part I) results in a charge neutralization and a gain in Kekulé resonance. The stability of (XV; X = S) and the instability of (XLII, Part I) is in agreement with this. It also explains why the higher stability of (XV; X = S) exceeds that of (III; X = S).

The inability to prepare (XV, Part II) compared with the ease of formation of (III; X = S) is also explicable. It is known that the $+M$ effect of a 3-substituted rhodanine nucleus is greater than that of a benzoyl group, as is shown by the higher nucleophilic reactivity of the $C_{(5)}$-atom of a rhodanine compared with that of the methyl group of acetophenone. Consequently (XV, Part II) should isomerize more readily to (XVI, Part II) than will (III; X = S) to (IV; X = S).

The high stability of the base (X; Part III) compared with (III; X = S) may also be explained similarly on the basis of the greater $+M$ effect of the benzoyl group compared with that of the 2-benzothiazolyl group. The quaternization of (X, Part III) to give (IV, $n = 0$; Part III) reverses the above conditions since the $+M$ effect of the positively charged 3-alkylbenzothiazolium nucleus is here considerably greater than that of a benzoyl group. The formation of the episulphide (VI; $n = 0$; Part III) is thus greatly facilitated and (IV; $n = 0$; Part III) is too unstable to exist.

From the above it is clear that the stability of open-chain sulphides of the type in which one bond is attached to a $-M$ group and the other to a $+M$ group will decrease as the strength of the M effects of these groups increases. If the assumption is made that the sulphur atom can function as a resonance transmitter, then only compounds with an energetically highly asymmetric resonance system can be stable. When the sulphur atom is part of a cyclic system, and when the two atoms attached to the sulphur atom can no longer approach one another sufficiently closely for bond formation between them to occur, then a stable compound would be expected irrespective of the degree of energetic asymmetry of its resonance system. Scott (*J. Amer. Chem. Soc.*, 1953, **75**, 6332) has, however, shown that 4 : 5-benzothiepin-2 : 7-dicarboxylic acid (XVIII), whilst stable in the solid state, readily decomposes in aqueous alcohol, or on fusion, to give naphthalene-2 : 3-dicarboxylic acid (XX) and sulphur (nacreous?). He states that, from models, the 7-membered ring is not planar. This would facilitate the approach of the carbon atoms attached to the sulphur atom and the consequent decomposition, possibly through the episulphide (XIX).



The Absorption Characteristics of Sulphides containing Conjugated M *Groups.*—(a) *Anhydro-(4-methyl-2-quinolylthio)acetic acid* (XXI) (Duffin and Kendall, *J.*, 1951, **734**; see also Part I). The broad absorption band in the blue region (Fig. 1) is somewhat sensitive to changes in solvent polarity (Table I). This sensitivity is an indication that the resonance

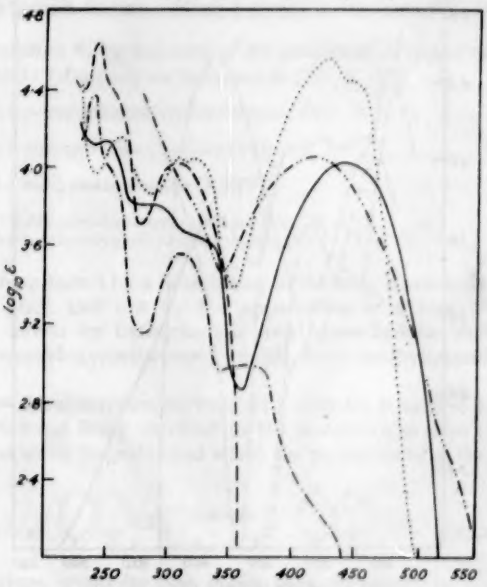
TABLE 1. *The absorption of the compound in various solvents.*

	C_6H_6	Pyridine	$CHCl_3$	$COMe_2$	MeOH	Aq. pyridine (1 : 1)
$\lambda_{max.}$ (mμ)	465	460	455	450	445	445
log ε	3·9	3·96	3·96	4·02	4·02	4·02

system responsible for the absorption in the long-wave-length band is of the charge-separation type represented by (XXI*a* ⟷ *c*) and not of the charge-transfer type (XXI*a* ⟷ *b*). The direction of the shift of $\lambda_{max.}$ indicates that the dipolar extreme structure (XXI*a*) is of lower energy than the non-polar structure (XXI*c*) (cf. Förster, *Z. Elektrochem.*, 1939, **45**, 572; Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, White, Crossman, and Dent, *J. Amer. Chem. Soc.*, 1951, **73**, 5332; Knott, *J.*, 1951, 3038) but the accompanying hyperchromic shift is the reverse of that expected.

The fragments of (XXI) on either side of the sulphur atom are contained in the 1-methyl-2-methylthioquinolinium salt (XXII) and in the anion (XXIII) of thioindoxyl.

FIG. 1. *Absorption in methanol of the compound* (XXI) *and related compounds.*



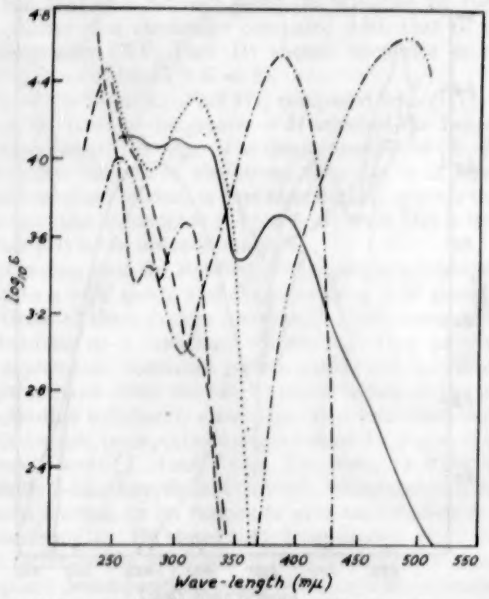
		$\lambda_{max.}$ (mμ), log ε (in parentheses), i = inflexion.
———	Anhydro-(4-methyl-2-quinolylthio)acetic acid (XXI)	250(4·14), 292(3·81), 325i(3·62), 445(4·02)
– – – –	1-Methyl-2-methylthioquinolinium toluene-*p*-sulphonate (XXII)	243(4·64), 307(4·02)
. . . . .	1 : 2-Dihydro-1-methyl-2-phenacylidenequinoline (VII)	262(4·16), 311(4·04), 321(4·04), 414i(4·44), 430(4·56), 451(4·45)
— · —	Thioindoxyl anion (XXIII)	241(4·37), 310(3·55), 367(3·1)
— · · —	2-Benzoylthiomethylene-1 : 2-dihydro-1-methylquinoline (VI; X = S)	420(4·05)

Their absorption curves (Fig. 1) clearly show that neither fragment in itself is responsible for the long-wave-length band of (XIX) and confirm the occurrence of an interaction (XXI*a* ⟷ *c*) between the two fragments through the sulphur atom. Analogues of (XXI) in which the sulphur atom is replaced by an oxygen atom or vinylene group have not been synthesized but comparison with 1 : 2-dihydro-1-methyl-2-phenacylidenequinoline (VII) indicates that the sulphur atom is in no way equivalent to a vinylene group as a chromophore. The closest relative of (XXI) so far obtained is 2-benzoylthiomethylene-1 : 2-dihydro-1-methylquinoline (VI; X = S) and, as Fig. 1 shows, there is a certain resemblance between their curves. Since the structural relation between these two compounds becomes closer with greater tendency of the sulphur atoms to conjugate, the similarity of the curves may again be an indication of such conjugation.

(b) 2-*Benzoylthiomethylene-3-methylbenzothiazoline* (III; X = S). The position of the long-wave-length band (Fig. 2) is practically insensitive to changes in solvent polarity. It is the same as for 3-methyl-2-phenacylidenebenzothiazoline (V; R = Me) which is also a decomposition product of (III; X = S). However, since this band of (III; X = S) fades it cannot be due to the presence of this stable decomposition product and must be considered to be a characteristic band of (III; X = S).

Because of the difficulty in purification, the absorption of 2-benzoyloxymethyl-3-methylbenzothiazoline (III; X = O) was measured on solutions obtained by treating the solution or suspension of its salt (II; X = O) with a base.* In methanol (Fig. 2) it showed

FIG. 2. *Absorption in methanol of the sulphide* (III) *and related compounds.*



———	2-Benzoylthiomethylene-3-methylbenzothiazoline (III; X = S)	260(4·13), 295(4·13), 320(4·09), 385(3·72)
– – – –	Phenacyl thiolbenzoate (XII)	238(4·44), 263i(2·99)
. . . . .	3-Methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S)	238(4·45), 314(4·32)
— · —	3-Methyl-2-phenacylidenebenzothiazoline (V)	250(4·01), 382(4·56)
— · · —	2-3′-Benzoylallylidene-3-methylbenzothiazoline (III; X = ·CH:CH·)	481(4·66)
– – · – –	2-Benzoyloxymethylene-3-methylbenzothiazoline (III; X = O)	275(3·45), 307(3·67)

the long-wave-length band at considerably shorter wave-length than that of the analogous band of (III; X = S). The curves for these compounds clearly show the bathochromic effect of proceeding from (III; X = O) to (III; X = S), an indication of conjugation through the sulphur atom in the latter compound.

The replacement of the chain-sulphur atom of (III; X = S) by a vinylene group to give 2-3′-benzoylallylidene-3-methylbenzothiazoline (III; X = ·CH:CH·) results in very strong bathochromic and hyperchromic shifts (Fig. 2). This is striking evidence of the resistance offered by the sulphur atom to the passage of an electron through its *d*-orbitals.

The fragments on either side of the chain-sulphur atom of (III; X = S) are contained in 3-methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S) and phenacyl thiolbenzoate (XII). A comparison of their absorption curves with that of (III; X = S) shows

* The same procedure was adopted for absorption measurements on (VI, XIII*a*, XIV*a*, and XV*a*; X = O).

that the long-wave-length band of the latter must be ascribed to the system (III*a* ⟷ *b*; X = S) in which the sulphur *d*-orbitals are utilized.

(c) *2-Benzoylthiomethylene*-1 : 2-*dihydro*-1-*methylquinoline* (VI; X = S). The absorption curves in benzene, *cyclo*hexane (Table 2), acetone, or ethyl acetate are almost identical, but in methanol strong hypsochromic and hypochromic shifts result, probably because of some chemical interaction with the solvent. The analogue in which the sulphur atom has been replaced by a vinylene group could not be obtained pure. Comparison of the curve of (VI; X = S) with that of its sulphur-free analogue, 1 : 2-dihydro-1-methyl-2-phenacylidenequinoline (VIII), shows the non-equivalence of the sulphur atom and a vinylene group.

Comparison of the curve for (VI; X = S) with that for 1 : 2-dihydro-1-methyl-2-*p*-tolylthiomethylenequinoline (XIV*a*; X = S) indicates that conjugation through the sulphur atom of the former occurs. Here, but not in the benzothiazoline series, however,

TABLE 2. *Absorption in* cyclo*hexane of the compound* (VI) *and related compounds.*

2-Benzoylthiomethylene-1 : 2-dihydro-1-methylquinoline (VI; X = S)	273(4·5), 308i(3·88), 321i(3·76), 410(4·07)
1 : 2-Dihydro-1-methyl-2-*p*-tolylthiomethylenequinoline (XIV; X = S)	280(4·32), 305i(4·15), 405(3·97)
1 : 2-Dihydro-1-methyl-2-phenacylidenequinoline (VII)	330(4·1), 410(4·39), 429(4·42), 453i(4·15)
1 : 2-Dihydro-1-methyl-2-methylenequinoline (XXIV)	283i(3·89), 317(3·63), 330(3·56), 389(3·6)
2-Benzoylmethylene-1 : 2-dihydro-1-methylquinoline (VI; X = O)	345(3·77), 410(3·82)
1 : 2-Dihydro-1-methyl-2-*p*-tolyloxymethylenequinoline (XIV; X = O)	406(3·73)

such conjugation is manifested by a broadening of the long-wave-length band accompanied by a hyperchromic shift and not by the appearance of a new band. This through-conjugation is also shown by bathochromic and hyperchromic shifts in the curves on proceeding from 2-benzoyloxymethylene-1 : 2-dihydro-1-methylquinoline (VI; X = O) to (VI; X = S).

Table 2 also shows the absorption curve of 1 : 2-dihydro-1-methyl-2-methylenequinoline, the long-wave-length band being ascribed to the resonance system (XXIV*a* ⟷ *b*). As in the benzothiazoline series (unpublished work) the replacement of the methylene group by

(XXIV*a*) (XXIV*b*)

a 2-*p*-tolylthiomethylene group (to give XIV; X = S) results in a strong hyperchromic shift. In this case, however, an appreciable bathochromic shift also occurs. This indicates that this band of (XIV; X = S) may be ascribed to the resonance system(XIV*a* ⟷ *b*; X = S) involving an expansion of the sulphur electron octet.

It is also noteworthy that similar, but smaller, bathochromic and hyp erchromic shifts result on passing from (XXIV) to the *p*-tolyloxy-derivative (XIV; X = O). Such a shift was not observed in the benzothiazoline series. Whether this implies that the presence of the tolyloxy-group decreases the energetic asymmetry of the system (XXIV*a* ⟷ *b*) by virtue of its $+I$ effect, or that the system (XIV*a* ⟷ *b*; X = O), involving the oxygen *d*-orbitals, is in operation, is not known. Since the $+I$ effect of sulphur is weaker than that of oxygen the larger shift shown by the introduction of the *p*-tolylthio-group compared with that of the *p*-tolyloxy-group confirms the origin of the long-wave-length band of (XIV; X = S).

(d) 3-*Methyl*-2-p-*nitrophenylthiomethylenebenzothiazoline* (XV; X = S). It has not been found possible to synthesize the related compound in which the chain-sulphur atom is replaced by a vinylene group. The lower vinylogue of the latter, 3-methyl-2-*p*-nitrobenzylidenebenzothiazoline (Part I) already shows, however (Table 3), by its longer-wave-length band that the chain-sulphur atom of (XV; X = S) is not effectively conjugated.

The compounds used for comparison (see Table 3) are 3-methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S) and *p*-methylthionitrobenzene. The peaks of (XV; X = S) at 325 mμ and of (XIII; X = S) at 314 mμ are probably due to the resonance

systems (XIII*a* ⟷ *b*). The long-wave-length band of *p*-methylthionitrobenzene does not appear in the spectrum of (XV; X = S) although it probably contributes to the band with the peak at 325 mμ. The inflexion at 415 mμ in the band of (XV; X = S) cannot be due to a simple displacement of the band of the the *p*-nitrophenylthio-group since it lies at a considerably lower intensity. The largest bathochromic displacement of the curve of the *p*-nitrophenylthio-group would be given by its anion which also has its $\lambda_{max.}$ at 415 mμ (Table 3) but at a considerably higher intensity than that of the inflexion of (XV; X = S).

TABLE 3. *Absorption in methanol of the compound* (XV; X = S) *and related compounds.*

3-Methyl-2-*p*-nitrophenylthiomethylenebenzothiazoline (XV; X = S)	234(4·43), 325(4·42), 415(3·45)
3-Methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S)	238(4·45), 314(4·32)
3-Methyl-2-*p*-nitrobenzylidenebenzothiazoline	485(4·47)
p-Methylthionitrobenzene	341(4·1)
p-Nitrothiophenoxide ion	415(4·16)

It is concluded, therefore, that this inflexion is, approximately, the peak of a new band arising from the system (XV*a* ⟷ *b*; X = S) in which the sulphur *d*-orbitals are engaged.

Brooker (Amer. Chem. Soc. Meeting, Autumn, 1937) prepared a dinitro-analogue of (XV; X = S) by the condensation of a 3-ethyl-2-methylbenzothiazolium salt with 2 : 4-dinitrobenzenesulphenyl chloride in pyridine and compared its absorption with that of the related compound in which the chain-sulphur atom was replaced by a vinylene group. The former has peaks at *ca.* 317 mμ (4·43) and *ca.* 472 (3·7) whilst the latter has a peak at *ca.* 583 mμ (4·2). From this Brooker concluded that this replacement substantially destroyed the main resonance system.

(e) 2-*Benzothiazol-2′-ylthiomethylene-3-methylbenzothiazoline* (XXV). Table 4 describes the absorption curves of this planar compound (Part III) with those for the related compounds in which the sulphur atom has been replaced by a vinylene group, as in (XXVI; *n* = 1),

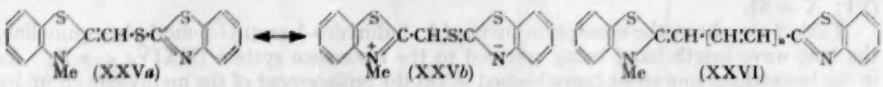


TABLE 4. *Absorption in methanol of compound* (XXV) *and related compounds.*

2-Benzothiazol-2′-ylthiomethylene-3-methylbenzothiazoline (XXV)	226(4·52), 236(4·54), 272(4·18), 318i(4·45), 326(4·49)
3-Methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S)	238(4·45), 314(4·32)
2-Benzothiazol-2′-ylmethylene-3-methylbenzothiazoline (XXVI; *n* = 0)	382(4·7), 395(4·7) *
2-3′-(Benzothiazol-2-yl)allylidene-3-methylbenzothiazoline (XXVI; *n* = 1) ...	451(4·73) †

Hamer (*J.*, 1940, 799) gives * 397(383i) mμ and † 455 mμ in methanol.

or eliminated, as in (XXVI; *n* = 0). This set again shows clearly how the chain-sulphur atom, by increasing the energetic asymmetry of the resonance system, causes hypsochromic and hypochromic shifts. A comparison of the absorption of (XXV) with that of 3-methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S) indicates a rather weak conjugation effect through the chain-sulphur atom. This is consistent with the weak +*M* effect of the benzothiazolyl group.

(f) 3-*Methyl*-2-p-*tolylsulphonylmethylenebenzothiazoline* (XIII; X = SO_2) *and* 1 : 2-*dihydro*-1-*methyl*-2-p-*tolylsulphonylmethylenequinoline* (XIV; X = SO_2). The absorptions of these sulphones in *cyclo*hexane are shown in Table 5 together with those of the related sulphides (XIII; X = S) and (XIV; X = S). In both cases the intensity of the long-wave-length band of the sulphone is higher than that of the related sulphide. In the

TABLE 5. *Absorption in* cyclo*hexane of the sulphone* (XVII) *and related compounds.*

3-Methyl-2-*p*-tolylsulphonylmethylenebenzothiazoline (XIII; X = SO_2)	329(4·53)
3-Methyl-2-*p*-tolylthiomethylenebenzothiazoline (XIII; X = S)	314(4·26)
1 : 2-Dihydro-1-methyl-2-*p*-tolylsulphonylmethylenequinoline (XIV; X = SO_2)	269(4·18), 293(4·82), 388(4·12)
1 : 2-Dihydro-1-methyl-2-*p*-tolylthiomethylenequinoline (XIV; X = S)	280(4·32), 305i(4·15), 405(3·97)

benzothiazoline series there is also a slight increase in $\lambda_{max.}$ but a sharper falling-off on the long-wave-length side. In the dihydroquinoline pair, however, the long-wave-length band of the sulphone is displaced hypsochromically from that of the sulphide.

Although the greater intensity for both sulphones may indicate contributions by structures such as (XIV*b*; X = SO_2), involving the sulphur *d*-orbitals, the accompanying hypsochromic shifts are the reverse of what would be expected. It is possible that these anomalous shifts are the result of an increase in the energetic asymmetry of the molecules on proceeding from the sulphide to the sulphone. Although such a change invariably results in a hypochromic shift (cf. Brooker *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 5332, 5350) when it is produced by a change in solvent polarity, in the present case an accompanying hyperchromic shift would be present as a result of the increase in the length of the conjugated path.

Such an increase in asymmetry could be brought about if the sulphone-oxygen atoms could not be freely accommodated without interference from the thiazole sulphur atom or the 3-hydrogen atom of the quinoline ring. There appears, however, from scale models, to be sufficient space available for the oxygen atoms on either side of these ring atoms.

The asymmetry would also be greater if the increase in the $+M$ effect of the anti-auxochrome on moving from $-S-$ to $-SO_2-$ were sufficiently great to make the polar extreme structure (*b*) of lower energy than the non-polar extreme structure (*a*). This would be more likely to occur in (XIV; X = SO_2) than in (XIII; X = SO_2) because of the higher $-M$ effect of the dihydroquinoline nucleus. Then the absorption of the sulphones should shift hypsochromically with increasing solvent polarity. This has been found to be the case although the shifts of $\lambda_{max.}$ on changing from *cyclo*hexane to methanol as solvent are extremely small (5 mμ).

Experimental

2-3′-Benzoylallylidene-3-methylbenzothiazoline (III; X = ·CH:CH·).—2 : 3-Dimethylbenzothiazolium toluene-*p*-sulphonate (3·35 g., 0·01 mole), sodium hydroxymethyleneacetophenone (2·5 g., 0·015 mole), and methanol (20 c.c.) were refluxed together for 10 min. An orange colour developed immediately and a solid *product* separated (1·8 g., 61·5%), forming orange-yellow needles, m. p. 168°, from benzene–light petroleum (b. p. 60—80°) (Found : N, 4·5; S, 11·05. $C_{18}H_{15}ONS$ requires N, 4·3; S, 10·9%).

2-Benzoylthiomethylbenzothiazole (I; X = S).—2-Bromomethylbenzothiazole (Zubarowski, *J. Gen. Chem. U.S.S.R.*, 1951, **21**, 2055) (2·3 g., 0·01 mole), potassium thiolbenzoate (1·8 g., 0·01 mole), and ethanol (20 c.c.) were heated together on a steam-bath for 5 min. Water (75 c.c.) was slowly run in, precipitating the *ester* which was collected after chilling and washed with water (yield, 2·5 g., 86%) and formed colourless flakes, m. p. 76—77°, from ethanol (Found : N, 4·9; S, 22·6. $C_{15}H_{11}ONS_2$ requires N, 4·9; S, 22·45%).

2-Benzoylthiomethyl-3-methylbenzothiazolium (*methyl sulphate*) (II; X = S) was obtained in 86% yield by heating the ester (I; X = S) (1·4 g.) with methyl sulphate (0·5 c.c.) for 1—2 min on the steam-bath. The whole solidified when seeded, otherwise solidification was induced by the addition of a little hot acetone to the resultant tar. The salt formed pale yellow flakes, m. p. 164—166°, from ethanol–ether (Found : N, 3·6; S, 23·6. $C_{17}H_{17}O_5NS_2$ requires N, 3·4; S, 23·35%).

2-Benzoylthiomethyl-3-ethylbenzothiazolium (*ethyl sulphate*) was obtained in 50% yield by similar use of diethyl sulphate (0·65 c.c.) (2 hr.). The tar crystallised as cream-coloured flakes, m. p. 166°, from ethanol (Found : N, 3·25; S, 22·1. $C_{19}H_{21}O_5NS_2$ requires N, 3·2; S, 21·85%).

2-Benzoylthiomethylene-3-methylbenzothiazoline (III; X = S).—The salt (II; X = S) (2·05 g., 0·005 mole) in methanol (10 c.c.) was treated at 25° with triethylamine (0·8 c.c., 0·005 mole). An intense yellow colour developed, followed by immediate crystallization of the *compound* (1·25 g., 83%), which formed yellow flakes, m. p. 117° (orange melt), from ethanol or light petroleum (b. p. 60—80°) (Found : C, 64·4; H, 4·3; N, 4·65; S, 21·2. $C_{16}H_{13}ONS_2$ requires C, 64·2; H, 4·35; N, 4·7; S, 21·4%). When it (0·2 g.) was refluxed for 10 min. with ethanol (5 c.c.) and triethylamine (0·1 c.c.) a red, microcrystalline solid separated (Found : S, 55·6%). The filtered solution on chilling gave an 81% yield of 3-methyl-2-phenacylidenebenzothiazoline (V), m. p. and mixed m. p. 176° (Found : S, 12·1. Calc. for $C_{16}H_{13}ONS$: S, 12·0%).

2-Benzoylthiomethylene-3-ethylbenzothiazoline was obtained in 88% yield as yellow needles, m. p. 100—101°, from light petroleum (b. p. 60—80°) (Found: N, 4·45; S, 20·75. $C_{17}H_{15}ONS_2$ requires N, 4·45; S, 20·45%). It liquefied at 25° in 1 week with the evolution of hydrogen sulphide. It was stable at 0—5°.

2-Benzoyloxymethyl-3-methylbenzothiazolium (Methyl Sulphate) (II; X = O).—2-Benzoyloxymethylbenzothiazole (Zubarowski, *loc. cit.*) (2·2 g.) and methyl sulphate (1·0 c.c.), when heated together on a steam-bath for 2 mins., fused, then solidified. The *salt* (2·95 g., 75%) formed needles, m. p. 188°, from ethanol (Found: C, 51·4; H, 4·35; S, 16·3. $C_{17}H_{17}O_6NS_2$ requires C, 51·6; H, 4·3; S, 16·2%).

Its alcoholic solution on treatment with triethylamine gave an intense, blue colour. Addition of water then precipitated a pale yellow oil, presumably 2-benzoyloxymethylene-3-methylbenzothiazoline, which did not crystallize and decomposed on attempted distillation. Refluxing it with alcoholic triethylamine did not give a crystalline product.

2-Benzoylthiomethylquinoline.—2-Bromomethylquinoline (Brown, Hammick, and Thewlis, *J.*, 1951, 1145) (5·55 g.), potassium thiolbenzoate (4·5 g.), and ethanol (50 c.c.) were refluxed together on a steam-bath for 1 hr. The required *compound* was precipitated with water and recrystallized from a little ethanol. It (4·2 g., 75%) formed orange brown flakes, m. p. 76°, from light petroleum (b. p. 60—80°) (Found: N, 5·05; S, 11·65. $C_{17}H_{13}ONS$ requires N, 5·0; S, 11·5%).

2-Benzoylthiomethylene-1:2-dihydro-1-methylquinoline (VI; X = S).—2-Benzoylthiomethylquinoline (1·4 g.) and methyl sulphate (0·5 c.c.) were heated together on a steam-bath for 3 min. The resulting light brown tar of *2-benzoylthiomethyl-1-methylquinolinium (methyl sulphate)* was washed with ether and kept at 5° for several days to crystallize. It was washed with acetone–ether (2:1) and obtained in low yield as plates, m. p. 105°, from ethanol–ether (Found: N, 3·35; S, 16·0. $C_{19}H_{19}O_6NS_2$ requires N, 3·45; S, 15·8%).

The crude tar of quaternary salt was dissolved in ethanol (5 c.c.), and triethylamine (0·8 c.c.) was added at 20°. The solution became intensely yellow and solidified. The solid *dihydroquinoline* (0·8 g., 54·5%) was washed with a little ethanol and obtained as orange flakes, m. p. 102°, from light petroleum (b. p. 60—80°) (Found: N, 4·6; S, 10·95. $C_{18}H_{15}ONS$ requires N, 4·8; S, 10·9%). It darkened on exposure to light.

The base (2·2 g.) was refluxed in ethanol (50 c.c.) and triethylamine (1·5 c.c.) for 1 hr. Hydrogen sulphide was liberated and a crystalline precipitate formed which after chilling was washed with cold ethanol, the yellow filtrate and washings being united. The crystals (0·45 g.) formed brown needles, m. p. 239° (darkens at 227°), from pyridine–ethanol (Found: C, 60·25; H, 4·3; N, 6·45; S, 29·25. $C_{23}H_{18}N_2S_4$ requires C, 60·3; H, 4·1; N, 6·4; S, 29·2%). It is believed to be 3:6-*di*-(1:2-*dihydro*-1-*methyl*-2-*quinolylidene*)-1:2:4:5-*tetrathia*cyclo*hexane* (VIII).

The yellow filtrates were diluted with water (200 c.c.) and chilled overnight. The crystalline precipitate (1·25 g.) was air-dried and obtained as orange needles (1·05 g., 53·5%), m. p. 112°, from light petroleum (b. p. 80—100°) (Found: C, 82·55; H, 5·55; N, 5·6. Calc. for $C_{18}H_{15}ON$: C, 82·75; H, 5·75; N, 5·35%). It is 1:2-dihydro-1-methyl-2-phenacylidenequinoline (VII) and gives no m. p. depression on admixture with a specimen prepared according to Vongerichten and Rotta's method (*Ber.*, 1911, **44**, 1419; they give m. p. 107—108°).

2-Benzoyloxymethylquinoline.—2-Bromomethylquinoline (13·8 g.), sodium benzoate (9 g.), ethanol (50 c.c.), and water (30 c.c.) were refluxed together on a steam-bath for 3 hr. Water (250 c.c.) was added, precipitating an oil which crystallized at 5° during 3 days. The sticky brown solid was washed with water by decantation and dissolved in hot light petroleum (b. p. 60—80°), and the solution was filtered and cooled to 25°, the solution being continuously freed from cloudiness by the addition of more petroleum. The *product* which separated during 24 hr. at room temperature was collected and the filtrate was concentrated. The cooling, clarification, and seeding were repeated. The total crop of yellowish needles, after four such concentrations, was 10·5 g., 61·0%. It formed needles, m. p. 50—51°, from petroleum (b. p. 60—80°) (Found: C, 77·4; H, 5·2; N, 5·2. $C_{17}H_{13}O_2N$ requires C, 77·5; H, 4·95; N, 5·3%).

2-Benzoyloxymethyl-1-methylquinolinium (Methyl Sulphate).—2-Benzoyloxymethylquinoline (1·35 g.) and methyl sulphate (0·5 c.c.) were fused together for 5 min. on a steam bath, the whole solidifying. The *salt* was dissolved in ethanol (20 c.c.), and ether (20 c.c.) was added to give crystals (1·45 g., 72·5%), which formed white needles, m. p. 147—148°, from ethanol (Found: N, 3·45; S, 8·05. $C_{19}H_{19}O_6NS$ requires N, 3·6; S, 8·2%). They were converted into a purple dye when refluxed in alcoholic triethylamine for 1 hr. The methyl sulphate (1·3 g.) was dissolved in methanol (50 c.c.), and triethylamine (0·5 c.c.) was added at 25°. An intense yellow colour

developed which faded as a pink precipitate formed. The solid *substance* was collected after 5 min. and washed well with methanol and water. It (1·45 g.) darkened on exposure to light and had m. p. 155° (purple melt) (Found: C, 77·8; H, 5·7; N, 4·95. $C_{16}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·05%).

2-p-*Tolylthiomethylbenzothiazole*.—2-Bromomethylbenzothiazole (4·6 g., 0·02 mole) was added to a solution of potassium hydroxide (1·12 g., 0·02 mole) and *p*-thiocresol (2·5 g., 0·02 mole) in ethanol (50 c.c.), at 40°. Potassium bromide separated and the reaction was completed by heating the mixture for 5 min. on a steam-bath. The required *sulphide* separated as a yellow oil on addition of water (250 c.c.). It solidified under ether (yield, 5·1 g., 94%) and formed flat, colourless needles, m. p. 62—64°, from light petroleum (b. p. 60—80°) (Found: N, 5·25; S, 23·8. $C_{15}H_{13}NS_2$ requires N, 5·15; S, 23·6%). The base (1·35 g.) and methyl sulphate (0·5 c.c.) on a steam-bath (1 min.) gave the *metho(methyl sulphate)* (0·95 g., 48%), white threads, m. p. 140—141°, from ethanol–ether (Found: N, 3·35; S, 23·95. $C_{17}H_{19}O_4NS_2$ requires N, 3·5; S, 24·2%).

3-*Methyl*-2-p-*tolylthiomethylenebenzothiazoline* (XIII; X = S).—The above metho(methyl sulphate) (1·0 g.) was treated in methanol (5 c.c.), cooled to 20°, with triethylamine (0·4 c.c.). The *base* separated immediately as a colourless cake (0·65 g., 91·5%) and formed colourless needles, m. p. 127°, from light petroleum (b. p. 60—80°) (Found: C, 67·3; H, 5·3; N, 4·95; S, 22·75. $C_{16}H_{15}NS_2$ requires C, 67·4; H, 5·25; N, 4·9; S, 22·5%).

2-p-*Nitrophenylthiomethylbenzothiazole*.—Sodium *p*-nitrophenyl sulphide (1·8 g.) was dissolved in hot ethanol (25 c.c.), the solution was cooled, and 2-bromomethylbenzothiazole (2·3 g.) was added. The orange colour was discharged rapidly and a crystalline precipitate formed. If the solution was heated a blue colour appeared. Water (25 c.c.) was added and the ochre *product* collected. It (2·65 g., 87·5%) formed orange flakes, m. p. 131°, from ethanol (Found: N, 9·1; S, 21·3. $C_{14}H_{10}O_2N_2S_2$ requires N, 9·25; S, 21·2%). The base (1·5 g.) and methyl sulphate (0·5 c.c.) in boiling benzene (5 c.c.) (30 min.) gave the *metho(methyl sulphate)* (1·6 g., 75%), white threads, m. p. 184° (decomp.), from ethanol (Found: N, 6·4; S, 22·4. $C_{16}H_{16}O_6N_2S_3$ requires N, 6·55; S, 22·4%).

3-*Methyl*-2-p-*nitrophenylthiomethylenebenzothiazoline* (XV; X = S).—The above metho-(methyl sulphate) (1·07 g.) was dissolved in hot methanol (25 c.c.) and the solution cooled to 25°. Triethylamine (0·4 c.c.) was added causing an immediate orange precipitate, the colour of which immediately changed to a deep violet. The *base* (0·7 g., 88·5%) formed violet needles, m. p. 170°, from benzene–ethanol (Found: C, 57·1; H, 3·85; N, 8·6; S, 20·1. $C_{15}H_{12}O_2N_2S_2$ requires C, 57·0; H, 3·8; N, 8·85; S, 20·3%). When triethylamine was added to a suspension of the quaternary salt in ethanol orange crystals were obtained. When the solution of the violet threads in benzene–ethanol was seeded with the orange crystals a mixture of orange flakes and violet threads resulted. When a benzene solution of the violet threads was diluted with light petroleum and seeded with the orange flakes the whole crystallized as orange flakes, m. p. 170° (Found: C, 57·2; H, 3·75; N, 9·1; S, 20·45%). The latter were readily converted into violet threads by recrystallization from ethanol or benzene–ethanol. A mixture of the two forms melted at 170°.

2-p-*Tolyloxymethylbenzothiazole*.—Potassium hydroxide (0·56 g.) was dissolved in ethanol (15 c.c.), and *p*-cresol (1·1 g.) was added followed by 2-bromomethylbenzothiazole (2·3 g.). The whole was refluxed for 15 min. and the required *compound* was precipitated by the addition of water. It (2·25 g., 88%) formed colourless needles, m. p. 114—115°, from light petroleum (b. p. 60—80°) (Found: N, 5·5; S, 12·75. $C_{15}H_{13}ONS$ requires N, 5·5; S, 12·55%). The *metho-(methyl sulphate)* formed very pale yellow needles, m. p. 154° (red melt), from ethanol–ether (Found: N, 3·6; S, 17·05. $C_{17}H_{19}O_5NS_2$ requires N, 3·7; S, 16·8%). Its solution in ethanol developed a blue colour on addition of triethylamine. Water then precipitated a pale yellow oil, presumably of 3-methyl-2-*p*-tolyloxymethylenebenzothiazoline (XIII; X = O) which could not be distilled without decomposition.

2-p-*Nitrophenoxymethylbenzothiazole* was obtained in 66·5% yield by the method used for the preparation of the *p*-tolyloxy-analogue, with *p*-nitrophenol (1·4 g.) replacing *p*-cresol. The compound formed small, colourless needles, m. p. 192°, from benzene (Found: N, 9·9; S, 11·35. $C_{14}H_{10}O_3N_2S$ requires N, 9·8; S, 11·2%). 3-*Methyl*-2-p-*nitrophenoxymethylbenzothiazolium (methyl sulphate)* was obtained by fusing the base (1·4 g.) and dimethyl sulphate (1·0 c.c.) at 130° for 10 min. The resultant tar was refluxed with benzene (10 c.c.) for 30 min., to give yellow grains which were dissolved in methanol (20 c.c.). Ether was slowly added to the solution to give a meal of yellow crystals (1·8 g., 87·5%). They formed yellow needles (changing to buff on exposure to light), m. p. 198° (violet melt), from methanol–ether (Found: N, 6·6; S, 15·7. $C_{16}H_{16}O_7N_2S_2$ requires N, 6·8; S, 15·55%). Addition of triethylamine to its alcoholic solution

gave violet crystals, m. p. 149°, of 3-*methyl*-2-p-*nitrophenoxymethylenebenzothiazoline* (XV*a*; X = O) which decomposed on attempted recrystallization from benzene (Found: C, 60·2; H, 4·4; N, 9·1; S, 10·8. $C_{15}H_{12}O_3N_2S$ requires C, 60·0; H, 4·0; N, 9·35; S, 10·65%).

1 : 2-*Dihydro*-1-*methyl*-2-p-*tolylthiomethylenequinoline* (XIV; X = S).—To a solution of potassium hydroxide (1·12 g.) and *p*-thiocresol (2·5 g.) in ethanol (20 c.c.) was added 2-bromomethylquinoline (4·4 g.), and the solution was gently warmed. An exothermic reaction set in and potassium bromide was precipitated. Water precipitated a brown oil which was dissolved in ether; the solution was dried and evaporated. The residual oil was extracted with hot light petroleum (b. p. 60—80), and the solvent distilled from the extracts. The residual oil was not purified.

It (5·6 g.) and methyl sulphate (2 c.c.) were heated together on a steam-bath for 2 min. or until quaternization set in, and the resulting tar was boiled with benzene (20 c.c.) to remove any unchanged material. The thick brown oil was dissolved in ethanol (20 c.c.), and triethylamine (4 c.c.) added at 25°. The orange solution was chilled overnight and the yellow crystals which had separated (0·8 g., 14·3%) were washed with ethanol. This *base* formed yellow needles, m. p. 88—89°, from methanol (Found: N, 4·85; S, 11·5. $C_{18}H_{17}NS$ requires N, 5·0; S, 11·45%).

2-p-*Nitrophenylthiomethylquinoline*.—2-Bromomethylquinoline (3·8 g.) was added to a solution of sodium *p*-nitrothiophenol (3·0 g.) in ethanol (50 c.c.). The deep orange colour was discharged and a thick meal of crystals separated. The whole was refluxed for 15 min., then chilled, and crystalline *sulphide* was collected. It (4·05 g., 80%) formed buff needles, m. p. 118°, from ethanol (Found: N, 9·2; S, 10·65. $C_{16}H_{12}O_2N_2S$ requires N, 9·45; S, 10·8%). 1-*Methyl*-2-p-*nitrophenylthiomethylquinoline* (*methyl sulphate*), obtained in 40% yield (steam-bath; 5 min.), formed buff needles, m. p. 191°, from methanol–ether (Found: N, 6·45; S, 15·2. $C_{18}H_{18}O_6N_2S_2$ requires N, 6·65; S, 15·15%).

1 : 2-*Dihydro*-1-*methyl*-2-p-*nitrophenylthiomethylenequinoline* (XVI; X = S) was obtained by adding triethylamine (0·3 c.c.) to a solution of the above quaternary salt (0·75 g.) in methanol (10 c.c.). The deep orange precipitate solidified rapidly. It (0·475 g., 86·5%) formed orange flakes, m. p. 149°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 8·9; S, 10·3. $C_{17}H_{14}O_2N_2S$ requires N, 9·05; S, 10·3%).

2-p-*Nitrophenoxymethylquinoline*, obtained in 73% yield by the method used for the benzothiazole analogue, formed white needles, m. p. 141—142°, from ethanol (Found: N, 9·8. $C_{16}H_{12}O_3N_2$ requires N, 10·0%). 1-*Methyl*-2-p-*nitrophenoxymethylquinolinium* (*methyl sulphate*), obtained in 76% yield, formed white needles, m. p. 192°, from methanol–ether (Found: N, 6·8; S, 8·05. $C_{18}H_{18}O_7N_2S$ requires N, 6·9; S, 7·9%). A dilute solution of this salt in ethanol developed an immediate orange colour with triethylamine. In more concentrated solutions the orange colour appeared momentarily on addition of triethylamine and was followed by the separation of a pink, light-sensitive solid. This was washed with methanol and water and dried in vacuum. 1 : 2-*Dihydro*-1-*methyl*-2-p-*nitrophenoxymethylenequinoline* (XVI*a*; X = O) formed a yellow powder, m. p. 136° (purple melt), darkening at 120° (Found: C, 69·0; H, 5·1; N, 9·1. $C_{17}H_{14}O_3N_2$ requires C, 69·3; H, 4·75; N, 9·5%).

2-p-*Tolyloxymethylquinoline* was obtained, as was the benzothiazole analogue, in 93% yield, as buff flakes, m. p. 94°, from ethanol (Found: N, 5·65. $C_{17}H_{15}ON$ requires N, 5·65%). 1-*Methyl*-2-p-*tolyloxymethylquinolinium* (*methyl sulphate*) (77% yield) formed white needles, m. p. 150—151°, from ethanol–ether (Found: N, 3·65; S, 8·55. $C_{19}H_{21}O_5NS$ requires N, 3·75; S, 8·55%). On its treatment in dilute alcohol with triethylamine a yellow colour developed; in more concentrated solution a light-sensitive solid, m. p. 108—112°, separated which decomposed on attempted recrystallization, namely, 1 : 2-*dihydro*-1-*methyl*-2-p-*tolyloxymethylenequinoline* (XIV*a*; X = O) (Found: C, 81·8; H, 6·45; N, 5·05. $C_{18}H_{17}ON$ requires C, 82·2; H, 6·45; N, 5·3%).

2-p-*Tolylsulphonylmethylbenzothiazole*.—2-Bromomethylbenzothiazole (4·6 g.), sodium toluene-*p*-sulphinate dihydrate (4·3 g.), and ethanol (25 c.c.) were refluxed for 15 min. The *sulphone* separated rapidly during this time. The solution was chilled and the crystals (4·15 g., 68·5%) were washed with water and ethanol. From ethanol they formed flat, colourless needles, m. p. 171—172° (Found: N, 4·76; S, 21·2. $C_{15}H_{13}O_2NS_2$ requires N, 4·65; S, 21·1%). The base (1·5 g.) and methyl sulphate (1·0 c.c.) in 10 min. on a steam-bath yielded 2·05 g. (95·5%) of 3-*methyl*-2-p-*tolylsulphonylmethylbenzothiazolium* (*methyl sulphate*), white flakes (from ethanol–ether), m. p. 189—191° (Found: N, 3·25; S, 22·4. $C_{17}H_{19}O_6NS_2$ requires N, 3·25; S, 22·4%).

3-*Methyl*-2-p-*tolylsulphonylmethylenebenzothiazoline* (XIII; X = SO_2).—The above quaternary salt (1·05 g.) was dissolved in methanol (10 c.c.), and triethylamine (0·4 c.c.) was added at

20°. The methylene *base* separated rapidly, was washed with ethanol, recrystallized from the same solvent, and obtained in 90% yield (0·7 g.) as white needles, m. p. 171° (Found: N, 4·4; S, 20·3. $C_{18}H_{15}O_2NS_2$ requires N, 4·4; S, 20·2%).

2-p-*Tolylsulphonylmethylquinoline.*—2-Bromomethylquinoline (1·1 g.), sodium toluene-*p*-sulphinate dihydrate (1·1 g.) and ethanol (10 c.c.) were refluxed together for 1 hr. Water (20 c.c.) was added and the buff needles (1·27 g., 85·5%) which separated were recrystallized from benzene–light petroleum (b. p. 60—80°). The *sulphone* formed almost colourless needles, m. p. 150—152° (Found: N, 4·7; S, 10·95. $C_{17}H_{17}O_2NS$ requires N, 4·7; S, 10·8%).

The base (1·5 g.) and methyl sulphate (1·0 c.c., 100% excess) were fused together on a steam-bath for 15 min. The solid, 1-*methyl*-2-p-*tolylsulphonylmethylquinolinium* (*methyl sulphate*) (1·9 g., 90%) recrystallized from ethanol–ether as white needles, m. p. 195° (softened at 185°) (Found: N, 3·5; S, 15·2. $C_{19}H_{21}O_6NS_2$ requires N, 3·3; S, 15·15%).

1 : 2-*Dihydro*-1-*methyl*-2-p-*tolylsulphonylmethylenequinoline* (XIV; X = SO_2).—The above quaternary salt (1·0 g.) was dissolved in methanol (5 c.c.), and triethylamine (0·4 c.c.) was added at 20°. The granular yellow precipitate (0·6 g., 82%) which separated rapidly was recrystallized, first from ethanol, then from benzene–light petroleum (b. p. 60—80°), and obtained as yellow grains, m. p. 159° (Found: N, 4·4; S, 10·25. $C_{18}H_{17}O_2NS$ requires N, 4·5; S, 10·3%).

Ultra-violet and visible absorption curves were determined in a Hilger Uvispek Spectrophotometer. The author thanks Mr. R. A. Jeffreys and Mrs. M. E. Weston for the preparation of certain intermediates, Mr. C. B. Dennis for analyses, and Mr. R. Searle for absorption measurements.

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Compounds containing Sulphur Chromophores. Part V. Complex Cyanines.*

By EDWARD B. KNOTT.

[Reprint Order No. 5687.]

Complex cyanines derived from 1 : 3-dithia*cyclo*pentan-4-one have been prepared. Their absorption spectra indicate that the thiol-ester (·CO·S·) bridge of the above nucleus functions as an efficient transmitter of electrons between the auxochromes of the dyes. The absorptions of these dyes have been compared with those of related complex cyanines derived from tetrahydroglyoxaline and thiazolid-4- and -5-one.

PREVIOUS Parts of this series * have been concerned with the synthesis of compounds designed to show that a sulphur atom, by expanding its electron octet and utilizing its *d*-orbitals, may function as a resonance transmitter and form part of a chromophoric system. The present paper deals with known and new dyes in which a sulphur atom, attached to a carbonyl group, may function as an electron transmitter without utilizing its *d*-orbitals.

In its simplest form the system to be considered is represented by the thiol ester (I*a*; X = S), the ester resonance (I*a* ⟷ I*b*) being a fundamental requirement for any electronic transition between A and B. A is a $-M$ group and B a $+M$ group or *vice versa*, and the extreme structures of the hybrid to be considered may then be represented by (I*a* ⟷ I*b*) and (I*c*) or (I*d*) respectively. Similar systems are equally feasible in which X in (I*a*) is an oxygen atom or an ·NR· group.

$$\underset{(Ia)}{A{\cdot}CO{\cdot}X{\cdot}B} \longleftrightarrow \underset{(Ib)}{A{\cdot}C(\bar{O}){:}\overset{+}{X}{\cdot}B} \longleftrightarrow \underset{(Ic)}{\bar{A}{:}C(\bar{O}){\cdot}\overset{+}{X}{\cdot}\bar{B}} \qquad \underset{(Id)}{\bar{A}{:}C(\bar{O}){\cdot}\overset{+}{X}{:}\bar{B}}$$

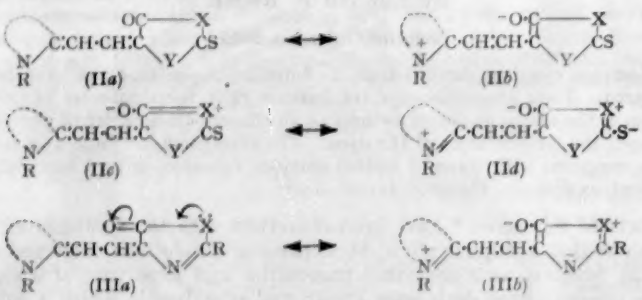
Cilento (*J. Amer. Chem. Soc.*, 1953, **75**, 3748) has described certain substituted phenyl thiolbenzoates (I*a*; A = *p*-NO_2·C_6H_4; B = *p*-MeO·C_6H_4; X = S). He assigned

* Parts I—IV, preceding papers.

absorption bands to four electronic transitions in the molecule, including one involving the sulphur *d*-orbitals, but did not consider transitions of the type (I*b* ⟷ I*d*). There is no evidence from his absorption curves (*loc. cit.*, Fig. 3) that such a transition occurs. This is perhaps not unexpected since, from models or scale drawings, it appears that the benzene ring in group B of (I*a*) is strongly crowded out of planarity with the rest of the molecule. The same non-planarity would also hinder or exclude contributions involving a sulphur decet.

The most suitable compounds for the examination of this effect, free from steric hindrance, are those containing a cyclic thiol-ester group. *mero*Cyanine dyes containing this group as part of a 3-substituted thiazolid-5-one nucleus (II*a*; X = S, Y = NR′) (Doyle, Lawrence, and Kendall, B.P. 622,775; Jeffreys and Knott, *J.*, 1952, 4632) or of a thiazol-5-one nucleus (III*a*; X = S) (Cook, Harris, and Shaw, *J.*, 1948, 1435; Aubert, Knott, and Williams, *J.*, 1951, 2185) are already available.

The long wave-length absorption band of *mero*cyanines is generally ascribed to the resonance system (II*a* ⟷ II*b*) (see, *e.g.*, Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, White, Cressman, and Dent, *J. Amer. Chem. Soc.*, 1951, **73**, 5332). This is indeed the fundamental system common to all such dyes. However, if a series of dimethin*mero*cyanines is considered, in which the basic nucleus remains constant but the ketonic nucleus varies, then it will be observed that the theoretical values of $\lambda_{max.}$ at the point of degeneracy of their resonance systems will vary greatly from case to case (cf. Brooker *et al.*, *loc. cit.*). This is often an indication that significant contributions are made by structures in which the electron passes beyond the ketonic oxygen atom. For (II*a*) where X = O, S, or NR it may be more accurate to represent the hybrid by (II*a* ⟷ II*b*) ⟷ (II*d*) with a similar system for (III*a*) in which X is a part of the main chromophoric chain. In general, except when Y is oxygen the ketonic nuclei which can function in this way give rise to the dyes with the deepest colours when their absorption is taken at the point of degeneracy.

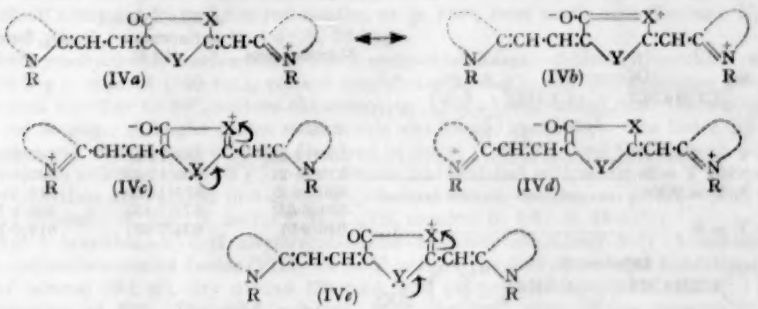


Impressive evidence of the truth of the above assumption is provided by the absorption characteristics of the complex cyanines (IV*a*) obtained by the replacement of the thionic sulphur atom of (II*a*) by a cationic residue. (Similar evidence which will not be discussed here is also provided by the related complex *mero*cyanines.) The synthesis of such dyes where X = S and Y = NR has been described by Doyle *et al.* (*loc. cit.*) and by Knott and Jeffreys (*J.*, 1952, 4762); where X = Y = NR by Riester and Willmanns (U.S.P. 2,440,119); and where X = NR, Y = S by Kendall (B.P. 487,051), Brooker (Mees, "The Theory of the Photographic Process," New York, Macmillan, 1942) and by Knott and Jeffreys (*loc. cit.*). The very large bathochromic and hyperchromic shifts obtained when we pass from (II*a*; X = S, Y = NR) to (IV*a*; X = S, Y = NR) have been ascribed by the last-named authors to the extension of the resonance system to give the hybrid represented by (IV*a* ⟷ IV*b*) ⟷ (IV*c*).

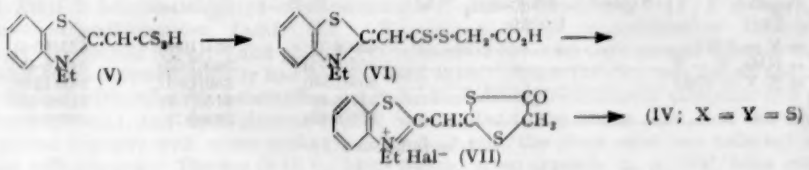
To complete the series of complex cyanines (IV*a*; X and Y = NR or S) the synthesis of (IV*a*; X = Y = S) was required. 2-Methylbenzothiazole ethiodide was condensed with carbon disulphide and triethylamine to give a solution of the salt of the acid (V) (cf. Kendall

and Majer, B.P. 549,201) and thence the acid ester (VI), which was cyclized by phosphorus trichloride or tribromide to the quaternary salt (VII). Condensation of (VII) at the reactive methylene group with a 2'-acetanilidovinyl derivative of a cyclic quaternary ammonium salt in an inert solvent then gave the required dyes—both (VII) and (IV; X = Y = S) are decomposed by hot alcohol or pyridine. A similar reaction series was carried out from 2-methylthiazoline methiodide.

As the Table shows, the changes in (IV*a*) from X = Y = NMe to X = S, Y = NMe to X = Y = S result in marked bathochromic shifts. The accompanying shifts in $\epsilon_{max.}$ do



not follow the same pattern, for all the dyes in which X = S, Y = NMe show substantially higher values than the other dyes. An increase in solvent polarity always results in a hypsochromic shift, particularly for those dyes in which X = S, Y = NR or S. This sensitivity to changes in solvent polarity is unusual in ionic dyes and must be ascribed in the present cases to the importance of dipolar contributing structures, particularly (IV*d*), in the hybrid. Any factor, such as an increase in solvent polarity which decreases



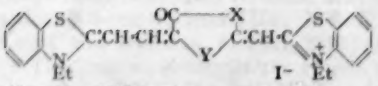
the energy of such excited structures will result in a hypsochromic shift (Knott, *J.*, 1951, 1024). Alternatively, since this increase in the significance of (IV*d*) will also increase the significance of the extreme structure (IV*a*), the hypsochromic solvent effect may be a result of increasing the energetic asymmetry of the dye by bringing the energy of (IV*c*) below that of (IV*a*). The fact that the hypsochromic shift is not always accompanied by a hypochromic shift does not agree, however, with this explanation.

The changes in the absorption of (IV*a*) on variation of X and Y are doubtless due in part to differences in the energetic asymmetry of the dyes. From a consideration of the values of ϵ, however, it appears that this factor can only be of minor importance. Much more probably such changes are due to changes in the relative energies of all the contributing resonance structures. If these are assessed empirically on the basis of the higher $-M$ effect of ·NMe· compared with that of ·S·, any change in X or Y from ·NMe· to ·S· will affect the energies of certain important excited structures represented by the curved arrows of (IV*c*) in much the same way as that of the hybrid extreme structure represented by the curved arrows of (IV*c*). Since these two factors tend to cancel out each other's effect on the absorption of the dye, a further factor must be considered which is not common to both excited and extreme structures. This may be the effect of changes in X and Y on the aromatic stabilization of the extreme structure (IV*c*) by the central nucleus. Thus it is known (Knott, *J.*, 1951, 1024) that any factor which decreases the

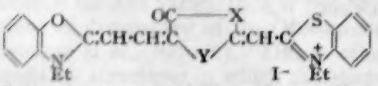
energy of an extreme structure with respect to that of an excited structure will result in a bathochromic shift.

If structures involving charged carbon atoms are neglected, then the central ring of (IV*c*) is stabilized by the contributions of the principal structures (XI*a* and *b*) when X = Y = NMe. The replacement of X = NMe by X = S then stabilizes the ring by allowing the additional structures (IX*d* and *f*) to participate by virtue of the ability of a

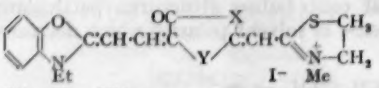
The absorption in solvents of different polarities of dyes (IV*a*).
($\lambda_{max.}$ *in* mμ, $10^{-4}\varepsilon$ *in parentheses.*)


(VIII)

	Nitrobenzene	*o*-Chlorophenol–acetone (1 : 4)	Aq. formamide (1 : 2)
X = Y = NMe	595(14·25)	588(12·4)	587(10·2)
X = NMe, Y = S	608(11·2)	600(11·45)	602(9·0)
X = S, Y = NMe	630(18·2), 584(6·55)	615(18·5), 572(7·45)	613(10·6), 569(5·7)
X = Y = S	646(9·0)	624(7·95)	615(5·1)


(IX)

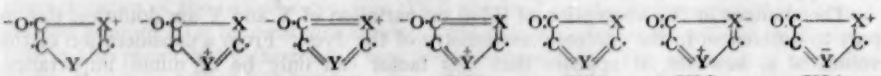
X = Y = NMe	558(9·85)	548(11·0)	550(10·4)
X = NMe, Y = S	580(7·85)	568(9·2)	570(7·7)
X = S, Y = NMe	591(17·9), 551(7·3)	570(21·2), 533(8·9)	572(13·7), 540(6·9)
X = Y = S	610(7·6)	600(7·9)	589(5·2)


(X)

X = Y = NMe	530(9·7)	524(10·8)	523(10·5)
X = NMe, Y = S	552(5·75)	540(7·05)	544(6·4)
X = S, Y = NMe	559(15·0), 527(6·8)	550(16·1), 515*i*(7·1)	548(13·0), 512(6·25)
X = Y = S	577(6·65)	568(6·7)	565(6·4)

(*i* = Inflexion.)

sulphur atom to expand its electron octet. The replacement of Y = NMe by Y = S allows structures (XI*c*, *e*, and *g*) to contribute in addition to (XI*a* and *b*), whilst in the dye where X = Y = S all the structures (XI*a*–*g*) contribute to the stabilization. This treatment would explain the differences found in the colour of the dyes with the exception that (IV*a*; X = NR, Y = S) would be deeper than (IV*a*; X = S, Y = NR).


(XI*a*) (XI*b*) (XI*c*) (XI*d*) (XI*e*) (XI*f*) (XI*g*)

The parent dye (II*a*; X = Y = S) from which (IX; X = Y = S) may be considered to be derived was synthesized some years ago by Dr. L. G. S. Brooker and in nitrobenzene it has $\lambda_{max.}$ 530 mμ (ε 6·5 × 10^4) (personal communication). The increase in ε on proceeding from this dye to (IX; X = Y = S) (ε 7·6 × 10^4) is much less than in the related dyes where X = S, Y = NMe. The evidence of interaction between electrons from either side of the sulphur bridges is shown, however, apart from the depth of colour of the complex dye by the strong effect on the absorption of a change in the nature of the right-hand nucleus, *e.g.*, from (IX) to (X) (see Table).

Experimental

Analyses are by Mr. C. B. Dennis.

2-(Carboxymethylthio)thiocarbonylmethylene-3-ethylbenzothiazoline (VI).—3-Ethyl-2-methylbenzothiazole toluene-*p*-sulphonate (28 g., 0·08 mole), ethanol (100 c.c.), carbon disulphide (6 c.c., 0·1 mole), and triethylamine (24 c.c., 0·16 mole) were heated to 60° and set aside for 30 min. Sodium chloroacetate (9·6 g., 0·083 mole) was added and the whole refluxed for 15 min. A cheesy mass separated. Water (400 c.c.) was added to dissolve most of the solid, and the solution was filtered and acidified with acetic acid. The orange crystals (20·4 g., 81·6%) which separated formed fine red needles, m. p. 198°, from acetic acid (Found: N, 4·6; S, 31·05. $C_{13}H_{13}O_2NS_3$ requires N, 4·5; S, 30·9%).

2-(Carboxymethylthio)thiocarbonylmethylene-3-methylthiazolidine.—2-Methylthiazoline methiodide (24·3 g.), ethanol (100 c.c.), carbon disulphide (7·0 c.c.), and triethylamine (30 c.c.) were warmed together to 60°, sodium chloroacetate (12·0 g.) was added, and the whole was refluxed for 20 min. A bright yellow sodium salt was formed gradually. The latter (16·5 g.) was collected and washed with ethanol, dissolved in water (100 c.c.), and the solution filtered to remove some yellow grains (2·3 g.). The filtrate was acidified with acetic acid. The yellow powder which then crystallized (6·6 g., 26·6%) formed brown needles, m. p. 175—176°, from acetic acid (Found: N, 5·5; S, 38·7. $C_8H_{11}O_2NS_3$ requires N, 5·6; S, 38·55%).

[3-Ethyl-2-benzothiazole][5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)-2-(1:3-dithiacyclopentan-4-one)]methincyanine Iodide (VIII; X = Y = S).—The finely powdered benzothiazoline thiol-ester (above) (3·1 g.), dry dioxan (30 c.c.), and phosphorus trichloride (1·5 c.c.) were ground together at 60°. The solid softened, then hardened after a few minutes. After chilling, the dioxan was decanted and the residual solid washed with ether by decantation. Finely ground 2-2′-acetanilidovinylbenzothiazole ethiodide (4·5 g.) was added, followed by cold methanol (100 c.c.) and triethylamine (1·8 c.c.). The whole was stirred for 5 min. and the solid was collected. It was dissolved in nitrobenzene (20 c.c.), and benzene (15 c.c.) was added to give 3·3 g. of *dye*. It (0·7 g., 11·5%) was obtained as black crystals, m. p. 275°, from nitromethane (Found: C, 47·4; H, 3·3; N, 4·4; I, 21·2; S, 21·3. $C_{24}H_{21}ON_3IS_4$ requires C, 47·3; H, 3·45; N, 4·6; I, 20·9; S, 21·05%).

[3-Ethyl-2-benzothiazole][5-(3-ethylbenzoxazolin-2-ylidene-ethylidene)-2-(1:3-dithiacyclopentan-4-one)]methincyanine Iodide (IX; X = Y = S).—The benzothiazoline thiol-ester (1·55 g.), dry dioxan (10 c.c.), and phosphorus tribromide (0·5 c.c.) were ground together until the solid which softened initially had become hard again. Ether (10 c.c.) was added and the solid washed with ether by decantation. 2-2′-Acetanilidovinylbenzoxazole ethiodide (2·2 g.), methanol (10 c.c.), and triethylamine (1 c.c.) were added to the above solid, and the whole was ground together with water cooling. After 2—3 min. the black solid was collected and washed with acetone. The *dye* (1·15 g., 39%) formed green crystals, m. p. 270°, from nitrobenzene (Found: C, 50·5; H, 3·7; N, 5·75; I, 17·45; S, 13·6. $C_{24}H_{21}O_5N_3IS_2,C_6H_5{\cdot}NO_2$ requires C, 50·3; H, 3·65; N, 5·85; I, 17·75; S, 13·45%). From nitromethane the solvent-free *product* formed green crystals, m. p. 262° (Found: N, 4·5; I, 21·7; S, 16·05. $C_{24}H_{21}O_2N_3IS_3$ requires N, 4·75; I, 21·4; S, 16·2%).

[4-(3-Ethylbenzoxazolin-2-ylidene-ethylidene)-1:3-dithia-2-cyclopentan-5-one][3-methyl-2-thiazoline]methincyanine Iodide (X; X = Y = S).—The thiazolidine thiol-ester (1·1 g.), dioxan (15 c.c.), and phosphorus trichloride (0·5 c.c.) were ground together at 25° to give a tar. This was washed with ether and ground at 25° for 3 min. with 2-2′-acetanilidovinylbenzoxazole ethiodide (2·0 g.), ethanol (15 c.c.), and triethylamine (0·7 c.c.). The *dye* was washed with ethanol and benzene and formed magenta threads (0·1 g., 4·3%) with a bronze reflex, m. p. 261°, from nitromethane (Found: N, 5·1; I, 24·1; S, 18·3. $C_{19}H_{19}O_2N_3IS_3$ requires N, 5·3; I, 23·95; S, 18·1%).

[3-Ethyl-2-benzothiazole][5-(3-ethylbenzothiazolin-2-ylidene-ethylidene)dihydro-1:3-dimethyl-4-oxo-2-glyoxaline]methincyanine Iodide (VIII; X = Y = NMe).—5-(3-Ethylbenzothiazolin-2-ylidene-ethylidene)-1:3-dimethyl-2-thiohydantoin (0·7 g.) and methyl sulphate (0·4 c.c.) were fused together on a steam-bath for 20 min. The solid quaternary salt was heated with 2-methylbenzothiazole ethotoluene-*p*-sulphonate (0·8 g.), pyridine (10 c.c.), and triethylamine (0·35 c.c.) on a steam-bath for 15 min. Saturated aqueous potassium iodide (1 c.c.) and then ethanol (25 c.c.) were added to the solution. The *dye* (1·1 g., 82%) crystallized on chilling and formed olive-green crystals, m. p. 275°, from methanol (Found: N, 9·2; I, 21·2; S, 10·6. $C_{26}H_{27}ON_4IS_2$ requires N, 9·3; I, 21·1; S, 10·6%).

[3-*Ethyl*-2-*benzothiazole*][5-(3-*ethylbenzoxazolin*-2-*ylidene*-*ethylidene*)*dihydro*-1:3-*dimethyl*-4-*oxo*-2-*glyoxaline*]*methincyanine iodide* (IX; X = Y = NMe) was obtained similarly and formed violet needles (62·5%), m. p. 253°, from methanol (Found: N, 9·4; I, 21·8; S, 5·7. $C_{36}H_{37}O_2N_4IS$ requires N, 9·55; I, 21·65; S, 5·45%).

[5-(3-*Ethylbenzoxazolin*-2-*ylidene*-*ethylidene*)*dihydro*-1:3-*dimethyl*-4-*oxo*-2-*glyoxaline*][3-*methyl*-2-*thiazoline*]*methincyanine iodide* (X; X = Y = NMe) was obtained in 68% yield as red needles, m. p. 251°, from methanol–ether (Found: N, 10·5; I, 24·3; S, 6·2. $C_{21}H_{25}O_2N_4IS$ requires N, 10·7; I, 24·25; S, 6·1%).

RESEARCH LABORATORIES, KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX.

[*Received, August 28th*, 1954.]

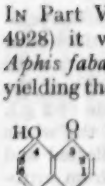
Colouring Matters of the Aphididae. Part XII. Addition Reactions of Erythroaphin-*sl *and its Conversion into Erythroaphin-*fb.

By B. R. BROWN, A. CALDERBANK, A. W. JOHNSON, S. F. MACDONALD, J. R. QUAYLE, and SIR ALEXANDER R. TODD.

[Reprint Order No. 5752.]

Diamino-, dihydroxy-, dipiperidino-, bis*cyclo*hexylamino-, and hydroxypiperidino-derivatives prepared from erythroaphin-*sl* are all identical with the corresponding derivatives from erythroaphin-*fb*. As they regenerate erythroaphin-*fb* after reduction with zinc and acetic acid, chemical methods are thus available for converting erythroaphin-*sl* into its *fb*-isomer. On the other hand, monohydroxy- and dibromo-erythroaphin-*sl* are distinct from the analogous compounds in the *fb*-series although both dibromoerythroaphins give one and the same dibromo-dipiperidinoerythroaphin on treatment with piperidine.

IN Part VII of this series (Brown, Johnson, MacDonald, Quayle, and Todd, *J.*, 1952, 4928) it was reported that erythroaphin-*fb*, one of the aphin pigments derived from *Aphis fabae* (Part II, *J.*, 1950, 477), readily reacted with ammonia, amines, and halogens, yielding the diamino-, *NN*-disubstituted diamino-, and dihalogeno-erythroaphins-*fb*, and with alkaline oxidising agents, giving dihydroxyerythroaphin-*fb*. This behaviour is consistent with the suggestion elaborated in earlier papers that the 4:9-dihydroxyperylene-3:10-quinone nucleus (I) is an integral part of the erythroaphin molecule and that it represents the sole chromophoric system of the latter. The aphins derived from *Tuberolachnus salignus* (Part III, *J.*, 1950, 485) are very similar to, but nevertheless distinct from, those from *A. fabae*. Thus not only is erythroaphin-*sl* isomeric with erythroaphin-*fb*, but the ultra-violet and visible spectra of both compounds are identical; only in their infra-red spectra do they show differences. Since it is evident that erythroaphin-*sl* must have the same chromophoric system as the *fb*-isomer it was decided to examine the reaction of the former with amines and halogens in the hope that it might throw further light on the relationship between the two series.



(I)

As expected, the reactions of erythroaphin-*sl* closely paralleled those of erythroaphin-*fb* but the surprising observation was made that the dihydroxy-, diamino-, dipiperidino-, and bis*cyclo*hexylamino-derivatives obtained were identical with those obtained from erythroaphin-*fb* (infra-red spectra); on reduction with zinc and acid they all yielded erythroaphin-*fb*. In this way it was possible to convert erythroaphin-*sl* into erythroaphin-*fb* and it is clear that conversion of the *sl*- into the *fb*- series occurs during production of the above disubstituted compounds.

On the other hand dibromoerythroaphin-*sl* was distinct from dibromoerythroaphin-*fb* and yielded erythroaphin-*sl* on reduction. Both these dibromo-derivatives, however, reacted with piperidine to produce one and the same dibromo-dipiperidinoerythroaphin

* Part XI, *J.*, 1954, 2378.

which we assign to the *fb*-series since it yielded, with zinc and acid, erythroaphin-*fb*; a similar merging of the two series is produced by reaction with ammonia and other amines. There is good evidence for the view that all four substituents in diamino-dibromo-erythroaphin-*fb* are located in the aromatic portion of the molecule. The introduction of the amino-groups must involve, in the first instance, addition to an activated double bond and on the basis of hydrogenation evidence (Parts II and III, *locc. cit.*) there are no non-aromatic double bonds in erythroaphin. Again, if bromination had occurred in the non-aromatic portion of the molecule, then the aliphatic bromine substituents would hardly be expected to survive the action of an excess of hot aqueous ammonia or amines. Attempts to halogenate the various diaminoerythroaphins or to dehalogenate the diamino-dibromoerythroaphins have not led to any clearly defined products.

In an effort to define more precisely the factors which bring about the isomerisation of the *sl*- to the *fb*-series, monohydroxyerythroaphin-*sl* was prepared by Thiele acetylation of the aphin followed by hydrolysis and re-oxidation; the product was distinct from monohydroxyerythroaphin-*fb* and had a different infra-red absorption spectrum. Both of these monohydroxy-compounds, however, with piperidine gave the same hydroxy-piperidinoerythroaphin, which from its behaviour on reduction is assigned to the *fb*-series. Simple reduction of erythroaphin-*sl* either with sodium dithionite or with zinc and aqueous sodium hydroxide, followed by reoxidation of the dihydro-compound either in alkaline solution or in acid suspension, failed to effect isomerisation, erythroaphin-*sl* being re-generated. Likewise none of the *fb*-isomer could be detected in the product obtained by acidifying an aqueous solution of the sodium salt of erythroaphin-*sl* after it had been kept at 0° for one hour (at higher temperatures hydroxylation of the molecule occurs very readily). No reaction products of either erythroaphin with hydrazoic acid, hydrogen cyanide, benzenesulphonic acid, hydrogen chloride, or hydrogen bromide have been characterised; either no reaction occurred or secondary reactions prevented isolation of the initial product.

The easy conversion of erythroaphin-*sl* into erythroaphin-*fb* by the various routes described in this paper, together with the remarkable similarity in physical and chemical properties of the two pigments strongly suggests that they are stereoisomeric substances. The isomerism, moreover, probably involves the configuration at one or more asymmetric centres in the non-aromatic portion of the erythroaphin molecule; both compounds are optically active and have widely different rotations. Detailed discussion of the optical activity of the pigments and their derivatives as well as of the precise nature of the changes involved in *sl* ⟶ *fb* conversions is deferred to a later paper (Part XIV, in the press) since it is necessary first to derive from the results of degradative studies the general structure of the erythroaphin molecule.

Experimental

Diaminoerythroaphin-fb.—A solution of erythroaphin-*sl* (500 mg.) in purified dioxan (200 c.c.) containing quinol (2 g.) and nitrobenzene (10 c.c.) was kept at 70° and aqueous ammonia (*d* 0·880; 25 c.c.) was added. The progress of the reaction was followed by partitioning small samples of the reaction mixture between chloroform and 10% hydrochloric acid. After 50 min. the solution was cooled and poured into light petroleum (b. p. 40—60°; 750 c.c.). The product was purified in the same manner as diaminoerythroaphin-*fb* (Part VII, *loc. cit.*) by partition between chloroform and 10% hydrochloric acid. The final chloroform extract was shaken overnight with saturated sodium hydrogen carbonate solution, and the precipitate, largely consisting of impurities, was separated and washed with a little chloroform. The chloroform solutions were concentrated and the volume maintained by addition of hot methanol; diaminoerythroaphin-*fb* (159 mg.) then separated as reddish-brown plates. For analysis it was recrystallised from the same solvents and dried at 40°/5 × 10^{-3} mm. (Found: C, 64·2; H, 4·2; N, 5·0. Calc. for $C_{20}H_{24}O_6N_2,H_2O$: C, 64·5; H, 4·7; N, 5·0%). Light absorption in $CHCl_3$ containing 5% of Et_2O: max. at 595, 567, 525, 487, 454, 429, 335, 322, and 255 mμ (log ε 3·77, 4·23, 4·05, 3·76, 4·54, 4·41, 3·63, 3·61, and 4·55 respectively). The infra-red spectrum, determined on a mull in Nujol, showed maxima at 697, 721, 762, 775, 833, 855, 921, 980, 997, 1017, 1053, 1064, 1081, 1163, 1202, 1239, 1289, 1577, 1629, and 3333 cm.$^{-1}$.

Dihydroxyerythroaphin-fb.—(i) *From diaminoerythroaphin*-fb. Diaminoerythroaphin-*fb*

(48·4 mg.; prepared from erythroaphin-*sl*) was treated with nitrous acid by the method described in Part VII (*loc. cit.*). The product (29 mg.) was separated, washed with ether and ethanol, and recrystallised from acetone as long red needles (Found, on a sample dried at 20°/10^{-3} mm.: C, 66·2; H, 4·2. Calc. for $C_{30}H_{22}O_{10}$: C, 66·4; H, 4·1%). Light absorption in $CHCl_3$: max. at 599, 572, 530, 494, 453, 428, 335, 322, and 252 mμ (log ε 3·76, 4·22, 4·05, 3·73, 4·62, 4·46, 3·66, 3·62, and 4·59 respectively). The infra-red spectrum of a mull in Nujol showed maxima at 700, 713, 737, 772, 834, 842, 870, 935, 946, 974, 1015, 1053, 1064, 1071, 1087, 1093, 1115, 1148, 1170, 1205, 1225, 1250, 1297, 1429, 1481, 1515, 1550, 1580, 1631, and 3333 cm.$^{-1}$.

(ii) *From erythroaphin*-sl. A solution of erythroaphin-*sl* (1·0 g.) and powdered potassium permanganate (2·0 g.) in pyridine (150 c.c.) containing a few drops of water was heated on a boiling water-bath for 2 hr. The precipitated manganese dioxide was separated and washed with hot pyridine, and the combined pyridine solutions were poured on ice (500 g.) and concentrated hydrochloric acid (200 c.c.). The red precipitate was extracted with chloroform (4 × 100 c.c.), and the chloroform extracts were washed with water and shaken thoroughly with N-sodium carbonate to extract the acidic product. The green aqueous layer was quickly washed with fresh chloroform and acidified with 3N-hydrochloric acid. The red precipitate was again extracted with chloroform, and the extract washed, dried, evaporated to small bulk (10 c.c.), and cooled to 0°. Dihydroxyerythroaphin-*fb* then separated as small deep-red needles (Found, in material dried at 100°/0·1 mm. for 6 hr.: C, 66·5, 66·4; H, 4·2, 4·0%). The ultra-violet and infra-red spectra of the product were identical with those recorded for the sample obtained by the preceding method.

Erythroaphin-fb *from Diaminoerythroaphin*-fb (cf. Part VII, *loc. cit.*).—Diaminoerythroaphin-*fb* (159 mg.; obtained from erythroaphin-*sl*) was reduced with zinc and acetic acid by the method described previously. After crystallisation from chloroform–ethanol, erythroaphin-*fb* (19 mg.) was obtained (Found: C, 70·5; H, 4·8. Calc. for $C_{30}H_{22}O_8$: C, 70·6; H, 4·4%). The ultra-violet and infra-red spectra agreed with those of authentic erythroaphin-*fb* (Parts II and V, *locc. cit.*).

Dipiperidinoerythroaphin-fb.—Erythroaphin-*sl* (110 mg.) was dissolved in freshly distilled piperidine (15 c.c.), and the dark green solution kept at room temperature for 3 hr.; a certain amount of crystalline product separated, and an examination (hand-spectroscope) of a chloroform extract of the acidified product (0·1 c.c.) showed that unchanged erythroaphin was no longer present. The main portion of the product was poured into 10% hydrochloric acid (ice), and the red precipitate extracted into chloroform (50 c.c., then 3 × 20 c.c.). The chloroform extract was washed with water and then 30% hydrochloric acid (3 × 30 c.c.) which removed very little of the coloured product from the chloroform. The pigment was extracted from the chloroform with 75% hydrochloric acid (5 × 30 c.c.), and the combined acid extracts were diluted with water (100 c.c.) and again extracted with chloroform (6 × 30 c.c.). The chloroform was then washed with water, then sodium hydrogen carbonate solution, and dried, and the solvent was removed. The reddish-brown residue was dissolved in pyridine (9 c.c.) and filtered, and warm aqueous methanol (15 c.c. of 80%) was added; the product crystallised as dark red plates (110 mg.) which were washed with methanol and dried. After two further crystallisations from pyridine–methanol the product (75 mg.) was dried for analysis at 90°/10^{-4} mm. for 5 hr. (Found: C, 71·0; H, 6·2; N, 4·3. Calc. for $C_{40}H_{40}O_8N_2$: C, 71·0; H, 6·0; N, 4·1%). The infra-red spectrum, which was identical with the product obtained from erythroaphin-*fb*, was determined on a Nujol mull and showed maxima at 738, 773, 817, 830, 846, 852, 862, 918, 934, 966, 995, 1020, 1042, 1073, 1096, 1117, 1149, 1183, 1198, 1261, 1280, 1307, 1570, 1600, and 1631 cm.$^{-1}$. Light absorption in $CHCl_3$: max. at 609, 575, 532, 445—448, 348, and 344 mμ (log ε 3·89, 4·24, 4·10, 4·28, 3·78, and 3·78 respectively) with an inflection at 328—336 mμ (log ε 3·70).

*Bis*cyclo*hexylaminoerythroaphin*-fb.—Erythroaphin-*sl* (100 mg.) was dissolved in freshly distilled *cyclo*hexylamine (15 c.c.) and kept for 3½ hr. The mixture was treated as in the foregoing experiment except that the extraction into hydrochloric acid was omitted. The solvent was removed from the final chloroform extract, the residue dissolved in pyridine (5 c.c.) and filtered, and crystallisation initiated by the addition of warm methanol (8 c.c.) containing 20% of 3N-hydrochloric acid. The product (90 mg.) which formed reddish-brown crystals was washed with methanol and then hot water and recrystallised from pyridine–methanolic hydrochloric acid as before. The dark red plates (70 mg.) were washed with hot water and dried at 90°/10^{-3} mm. for 9 hr. (Found: N, 5·1, 5·1. $C_{42}H_{44}O_8N_2,C_5H_5N$ requires N, 5·4%). The *compound* was further dried at 115°/10^{-4} mm. for 12 hr. (Found: N, 4·1. Calc. for

$C_{42}H_{44}O_8N_2$: N, 4·0%). **Light absorption** in chloroform: max. at 602, 572, 530, 462, and 253—254 mμ (log ε 3·88, 4·15, 4·04, 4·31, and 4·61 respectively), with an inflection at 332—334 mμ (log ε 3·93). The infra-red spectrum, which was identical with the product obtained from erythroaphin-*fb*, showed maxima (Nujol mull) at 1631, 1587, 1302, 1287, 1255, 1178, 1117, 1075, 1043, 990, 913, 889, 870, 857, and 825 cm.$^{-1}$.

Erythroaphin-fb *from Bis*cyclo*hexylaminoerythroaphin*-fb (cf. Part VII, *loc. cit.*).—Reduction of bis*cyclo*hexylaminoerythroaphin-*fb* (90 mg.; prepared from erythroaphin-*sl*) with zinc and acetic acid by the method already described gave erythroaphin-*fb* (22 mg.), the infra-red spectrum of which was identical with that of an authentic specimen.

Dibromoerythroaphin-sl.—Erythroaphin-*sl* (281 mg.) was suspended in glacial acetic acid (20 c.c.), and bromine (0·5 c.c.) added. The suspension was shaken for 1 hr. and then poured into water (200 c.c.). The *bromo-compound* which was precipitated was separated on the centrifuge, washed, dried (353 mg.), and crystallised twice from chloroform–ethanol as dark red plates (191 mg.). For analysis it was dried for 6 hr. at 75°/0·1 mm. (Found: C, 53·5; H, 3·0. $C_{30}H_{20}O_8Br_2$ requires C, 53·9; H, 3·0%). Light absorption in $CHCl_3$: max. at 566, 525, 454—456, 345, and 264 mμ (log ε 4·35, 4·21, 4·51, 3·70, and 4·70 respectively), with inflections at 472—476 and 330—340 mμ (log ε 4·45 and 3·66). The infra-red spectrum of a mull in Nujol showed maxima at 667, 771, 809, 824, 838, 851, 866, 917, 962, 977, 1001, 1047, 1081, 1117, 1136, 1163, 1198, 1241, 1304, 1344, and 1626 cm.$^{-1}$. The infra-red spectrum of dibromoerythroaphin-*fb* (Part VII, *loc. cit.*) also determined as a mull in Nujol showed maxima at 666, 755, 806, 829, 847, 870, 904, 935, 957, 1000, 1049, 1076, 1105, 1156, 1199, 1232, 1258, 1307, 1567, and 1626 cm.$^{-1}$; light absorption in chloroform: max. at 566, 525, 476, 452, 347, and 264 mμ (log ε 4·29, 4·15, 4·38, 4·43, 3·64, and 4·63 respectively), with inflections at 342—344 and 334—336 mμ (log ε 3·64 and 3·63).

Erythroaphin-sl *from Dibromoerythroaphin*-sl.—The dibromo-compound (180 mg.) was suspended in glacial acetic acid (200 c.c.), and zinc dust (40 g.) added. The mixture was heated on the water-bath for 15 min., the excess of zinc separated, and the filtrate cooled and diluted with water. The pigment was extracted into chloroform, and the chloroform shaken with sodium hydrogen carbonate solution. Further purification was effected by transferring the pigment from the chloroform into 72% sulphuric acid and then back into chloroform by diluting the sulphuric acid to 64% (Part III, *loc. cit.*). The chloroform was washed with sodium hydrogen carbonate solution and then water, dried, and concentrated. Hot ethanol was added to induce crystallisation and the product (40 mg.) was recrystallised from chloroform–ethanol (Found, in material dried at 100°/0·1 mm. for 4 hr.: C, 70·6; H, 4·5%). The infra-red spectrum (Nujol mull) was identical with that of authentic erythroaphin-*sl* (Part V, *loc. cit.*).

Dibromodipiperidinoerythroaphin-fb.—(i) *From dibromoerythroaphin*-sl. A solution of dibromoerythroaphin-*sl* (87 mg.) in pyridine (20 c.c.) and piperidine (2 c.c.) was kept overnight at room temperature and then poured into ice-cooled 10% hydrochloric acid. The solution was extracted into chloroform, and the chloroform solution washed with water and then shaken with 10N-hydrochloric acid (5 × 25 c.c.). The combined acid extracts were diluted with water (70 c.c.) and the pigment was extracted back into chloroform (6 × 25 c.c.). The combined chloroform extracts were washed with water, dried, and concentrated and crystallisation was induced by the addition of hot ethanol. The *product* (54 mg.) which formed dark red oblong crystals was recrystallised from chloroform–ethanol and for analysis was dried for 6 hr. at 70°/0·1 mm. (Found: C, 56·5, 56·4; H, 4·7, 4·3; N, 3·3. $C_{40}H_{34}O_8N_2Br_2,H_2O$ requires C, 56·4; H, 4·7; N, 3·3; Br, 18·7%). The water of crystallisation was not removed after drying at 110°/0·1 mm. overnight (Found: C, 56·8; H, 4·3%). Light absorption in $CHCl_3$: max. at 577—578, 534—535, 495, 351, and 265—266 mμ (log ε 4·34, 4·28, 4·32, 3·67, and 4·57 respectively), with an inflection at 334—337 mμ (log ε 3·68). The infra-red spectrum determined on a mull in Nujol showed maxima at 665, 680, 767, 786, 808, 847, 917, 950, 1024, 1036, 1078, 1111, 1171, 1183, 1212, 1244, 1277, 1567, and 1629 cm.$^{-1}$.

(ii) *From dibromoerythroaphin*-fb. The foregoing experiment was repeated with dibromoerythroaphin-*fb* (115 mg.). The product (91 mg.) was dried at 100°/0·1 mm. for 6 hr. for analysis (Found: C, 56·5; H, 4·4; N, 3·3; Br, 18·6%). The infra-red curve (determined on a mull in Nujol) was identical with that of the product of the previous experiment.

Erythroaphin-fb *from Dibromodipiperidinoerythroaphin*-fb.—The dibromo-compound (167 mg.) was debrominated and the product purified by the method used for dibromoerythroaphin-*sl*. The erythroaphin-*fb* (28 mg.) crystallised from chloroform–ethanol as before (Found, on a sample dried at 80°/0·1 mm.: C, 70·4; H, 4·6%). The infra-red spectrum (Nujol mull) was identical with that of authentic erythroaphin-*fb* (Part V, *loc. cit.*).

Diaminodibromoerythroaphin-fb.—A solution of dibromoerythroaphin-*fb* (105 mg.) in dioxan (60 c.c.) containing water (5 c.c.) and quinol (300 mg.) was kept at 70° under reflux for 1½ hr. while a stream of ammonia and another of air were bubbled through it. The mixture was cooled, diluted with water, and washed with light petroleum (b. p. 40—60°; 2 × 200 c.c.). The aqueous layer was acidified with hydrochloric acid (50 c.c. of 10%) and filtered and the filtrate partially neutralised with 10% sodium hydroxide solution (35 c.c.). The pigment was then extracted into chloroform (50 c.c., then 3 × 25 c.c.) and purified by extraction into 10% hydrochloric acid (6 × 25 c.c.) and then back again into chloroform (2 × 50 c.c.) after partial neutralisation with 10% sodium hydroxide solution (100 c.c.). The chloroform solution was washed and dried and the solvent removed. The residue was crystallised twice from a mixture of pyridine (10 c.c.), methanol (7 c.c.), and 10% hydrochloric acid (3 c.c.). *Diaminodibromoerythroaphin*-fb was thus obtained in black plates with a green lustre (Found, on a sample dried for 6 hr. at 90°/0·1 mm.: C, 54·8; H, 3·9; N, 5·1; Br, 20·7. $C_{30}H_{32}O_8N_2Br_2,C_5H_5N$ requires C, 54·1; H, 3·5; N, 5·4; Br, 20·6%). Light absorption in chloroform: max. at 570, 527, 480, 347, 333, and 264 mμ (log ε 4·23, 4·14, 4·45, 3·74, 3·71, and 4·63 respectively). The infra-red spectrum, determined on a mull in Nujol, showed maxima at 666, 703, 744, 762, 787, 802, 826, 858, 893, 935, 948, 1000, 1029, 1053, 1068, 1083, 1103, 1183, 1235, 1282, 1307, 1575, and 1631 cm.$^{-1}$.

Hydroxyerythroaphin-sl.—Erythroaphin-*sl* (500 mg.) was added to cold acetic anhydride (100 c.c.) containing perchloric acid (10 drops of 60%) and the mixture stirred at 0° for 6½ hr. The intermediate dihydro-hydroxyerythroaphin-*sl* penta-acetate was extracted and hydrolysed as described for the *fb*-isomer (Part VII, *loc. cit.*), *hydroxyerythroaphin*-sl (220 mg.) being obtained as slender red needles after crystallisation from chloroform–ethanol or from acetone (Found, on material dried at 110°/0·7 mm. for 24 hr.: C, 68·1; H, 4·5. $C_{30}H_{32}O_9$ requires C, 68·4; H, 4·2%). The light absorption of a solution in chloroform was identical with that of the *fb*-isomer, as were the general chemical properties. The infra-red spectrum of a mull in Nujol showed maxima at 721, 741, 766, 827, 840, 887, 942, 947, 1001, 1070, 1079, 1093, 1166, 1209, 1250, 1292, 1477, 1511, 1587, 1631, and 3226 cm.$^{-1}$, *i.e.*, was identical with that of hydroxyerythroaphin-*fb* (Part VII, *loc. cit.*) except for the absence of the band at 867 cm.$^{-1}$. (The band at 787 cm.$^{-1}$ previously reported in the infra-red spectrum of hydroxyerythroaphin-*fb* is now known to be due to an impurity and it should therefore be deleted from the figures there quoted.)

Monohydroxymonopiperidinoerythroaphin-fb.—(i) *From hydroxyerythroaphin*-sl. Hydroxyerythroaphin-*sl* (100 mg.) was dissolved in a mixture of pyridine (5 c.c.) and piperidine (5 c.c.) and kept at room temperature for 24 hr. The resulting deep green solution was added to 3N-hydrochloric acid at 0°, the cherry-red product extracted with chloroform, the extract washed with water and dried, and the solvent removed. The residue was crystallised repeatedly from chloroform–methanol, giving *monohydroxymonopiperidinoerythroaphin*-fb as deep red plates (Found, on a sample dried at 100°/2 × 10^{-4} mm. for 24 hr.: N, 2·2. $C_{35}H_{31}O_9N$ requires N, 2·3%). Light absorption in $CHCl_3$: max. at 564, 529, 448, and 336 mμ (log ε 4·14, 4·05, 4·33, and 3·83 respectively). The infra-red spectrum of a mull in Nujol showed maxima at 722, 749, 850, 926, 985, 1067, 1111, 1144, 1175, 1203, 1577, 1629, and 3289 cm.$^{-1}$.

(ii) *From hydroxyerythroaphin*-fb. By a similar process hydroxyerythroaphin-*fb* (97 mg.) yielded monohydroxymonopiperidinoerythroaphin (40 mg.), the infra-red spectrum of which was identical with that of the product from the previous experiment.

Erythroaphin-fb *from Monohydroxymonopiperidinoerythroaphin*-fb.—By reduction with zinc and acetic acid by the method used for dibromodipiperidinoerythroaphin-*fb* (above), monohydroxymonopiperidinoerythroaphin-*fb* (74 mg.) yielded erythroaphin-*fb* (15 mg.) as red needles from chloroform–ethanol. For analysis, the product was dried at 120°/10^{-3} mm. for 8 hr. (Found: C, 70·6; H, 4·4%). The infra-red spectrum, determined on a Nujol mull, was identical with that of authentic erythroaphin-*fb*.

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Colouring Matters of the Aphididae. Part XIII. The Structure of the Erythroaphins.*

By B. R. Brown, A. Calderbank, A. W. Johnson, B. S. Joshi, J. R. Quayle, and Sir Alexander R. Todd.

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Consideration of all available evidence leads to the conclusion that two structural formulæ, differing from each other in the location of an angular methyl group, are possible for erythroaphin. These structures contain two dioxan rings fused to a tetrahydrocoronene nucleus and additional support for them is provided by infra-red spectroscopic evidence. The stereochemical difference between erythroaphin-*fb* and erythroaphin-*sl* remains to be discussed.

The colouring matters of the *Aphididae* which we have described as aphins present structural problems of peculiar complexity. The glucosidic water-soluble protoaphin present in the haemolymph of the living insect is converted rapidly by enzyme action after the death of the insect into a yellow fat-soluble xanthoaphin, and thence through an orange chrysoaphin into the end-product, a relatively stable deep red erythroaphin (Part I, *Nature*, 1948, **162**, 759). Examination of some thirty species of coloured aphids has revealed the existence of at least two series of aphins (Parts IV and V; *J.*, 1950, 3304; 1951, 2633) which have been distinguished by the use of a suffix indicative of the commonest species from which they have been isolated; thus there are the aphins-*fb*, first isolated from *Aphis fabae* parasitic on broad beans (Part II, *J.*, 1950, 477), and the aphins-*sl* from the willow aphid *Tuberolachnus salignus* (Part III, *J.*, 1950, 485). Only the aphins-*fb* and -*sl* have as yet been examined by us in any detail, mainly for reasons of accessibility, and apart from determination of the glucosidic character of the protoaphins, attention has been largely concentrated on the erythroaphins. It seemed clear that only by elucidating the structure of the erythroaphins would the way be opened to an understanding of the remarkable series of changes leading to their formation from protoaphin—a series which, as far as we are aware, has no analogy in the field of natural colouring matters.

Much of the evidence necessary to establish the structure of the erythroaphins has already been published in earlier papers of this series. It is the purpose of the present communication to interpret this evidence and to amplify it in certain respects so that structural formulæ may be advanced for the erythroaphins. As has already been reported, the erythroaphins-*fb* and -*sl* are isomeric compounds $C_{30}H_{22}O_8$ having identical ultra-violet and visible absorption spectra but differing in infra-red absorption, solubility, and crystalline habit, and in optical rotation. Their extraordinary similarity in chemical behaviour, coupled with the fact that they both yield identical diamino- and dihydroxy-derivatives converted by the action of zinc and acetic acid into erythroaphin-*fb* (Part XII, preceding paper), makes it certain that the difference between the two pigments is stereochemical. This fortunate circumstance enables us first to consider evidence derived from studies on either pigment and to deduce from it a general structure for erythroaphin; the stereochemical difference between them and the mechanism of their interconversion form the subject of the following communication.

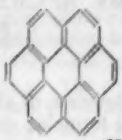
There can be no reasonable doubt that the erythroaphins are derivatives of 4 : 9-dihydroxyperylene-3 : 10-quinone (I). Evidence leading to this conclusion comes (1) from infra-red spectroscopic studies (Part V, *loc. cit.*), (2) from the production of perylene derivatives on zinc-dust fusion (Part VIII, *J.*, 1954, 107) and of mellitic acid on oxidation (Parts II and III, *locc. cit.*), (3) from analogies in chemical behaviour between the erythroaphins, perylene-3 : 10-quinone (Part IX, *J.*, 1954, 1280) and particularly 4 : 9-dihydroxyperylene-3 : 10-quinone (Part X, *J.*, 1954, 1285), and (4) from the observed close similarity between the absorption spectra of the tetra-acetyldihydroerythroaphins and perylene

* Part XII, preceding paper.

(Part VIII, *loc. cit.*) on the one hand and the erythroaphins and 4 : 9-dihydroxyperylene-3 : 10-quinone on the other (Part X, *loc. cit.*). Equally it is clear that the sole chromophoric system in the molecule is that of 4 : 9-dihydroxyperylene-3 : 10-quinone (I).

(I)

(II)


(III)

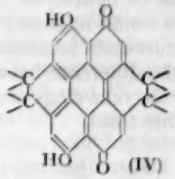
Zinc dust fusion of erythroaphin-*sl* (Part VIII, *loc. cit.*) yielded, not only perylene derivatives, but also derivatives of 1 : 12-benzoperylene (II) and of coronene (III). From this it may be concluded with some certainty that in erythroaphin the perylene system must bear carbon substituents on *at least* two of the central positions in the molecule, *i.e.*, at least one at position 1 or 12 and the other at position 6 or 7. Further, the fact that the erythroaphins yield a diamino-dibromoerythroaphin in which the substituents are attached to the chromophoric system (Part VII, *J.*, 1952, 4928; Part XII, *loc. cit.*) indicates that positions 2, 5, 8, and 11 in the perylene nucleus of erythroaphin are unsubstituted. Steric considerations would preclude entry of a bromine atom or an amino-group into either of the vacant central positions if one out of each of the pairs 1—12 and 6—7 were already occupied.

4 : 9-Dihydroxyperylene-3 : 10-quinone has a formula $C_{20}H_{10}O_4$ whereas erythroaphin has a formula $C_{20}H_{22}O_8$. It is clear from the evidence of hydrogenation that the erythroaphin molecule contains no unsaturation apart from that represented in the dihydroxyperylenequinone nucleus. Moreover, apart from the two hydroxyl and two quinonoid carbonyl groups it contains neither hydroxyl nor carbonyl groups, as shown by infra-red spectroscopic evidence and the failure of all attempts to make derivatives. The conclusion that the 4 " missing " oxygen atoms in erythroaphin must be present in ether linkages seems inescapable. At the same time the generally negative outcome of Zeisel determinations indicates that the 4 oxygen atoms are not present in methoxy-groups. Small non-stoicheiometric amounts of silver iodide which are formed in Zeisel determinations carried out under extreme conditions do not invalidate this statement; their origin will be discussed later.

If we now make the minimum deduction from the results of zinc dust fusion of erythroaphin-*sl*, *viz.*, that the dihydroxyperylenequinone system bears additional substituents only in positions 1 (or 12) and 6 (or 7), we are left with the problem of accommodating in these two substituents the residue $C_{10}H_{14}O_4$ which, being saturated and containing only ethereal oxygens, must contain 4 rings. Now the erythroaphins show no peroxidic properties so that the absence of C·O·O·C groupings may be reasonably inferred; nor, as above indicated, do they contain methoxy-groups. Application of the Kuhn–Roth procedure for the estimation of *C*-methyl to the erythroaphins (Parts II and III, *locc. cit.*) consistently yields some 3·8 mols. of acetic acid. Excluding, then, C·O·O·C and methoxy-groupings, and allowing for 4 *C*-Me groups (or their equivalent), it can be seen that the task of accommodating the saturated residue $C_{10}H_{14}O_4$ on the basis of a two-point, or even three-point, attachment is well-nigh impossible, and it must be concluded that the perylene nucleus in the erythroaphins is substituted in all four positions 1, 6, 7, and 12. Further, if we are to accommodate four rings, each at least five-membered, in the " missing " part of the molecule, it is necessary to assume that two of these rings are formed by joining $C_{(1)}$ to $C_{(12)}$ and $C_{(6)}$ to $C_{(7)}$ in each case by two atoms, and in all probability by two carbon atoms. The possibility that one of the junctions might be effected by one carbon and one oxygen atom leads to the postulation of highly unsymmetrical or otherwise unsatisfactory structures; it seems to us preferable to consider, first, more or less symmetrical structures for the pigments and therefore to expand the erythroaphin partial structure to (IV).

Taking into account the above facts and inferences it becomes apparent that if the erythroaphins are symmetrical only structures (V) and (VI) could occur on each side of the

perylene system between positions 1 and 12, and 6 and 7. Other arrangements (*e.g.*, seven-membered ring systems and others without an angular methyl group) are excluded either by inability to explain the results of *C*-methyl determinations, the production of alkylcoronene derivatives on zinc dust fusion, or the failure of the erythroaphins to dehydrogenate extremely readily yielding true coronenes. It is known that dioxan yields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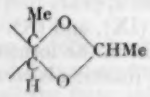
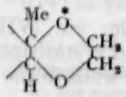

(V)

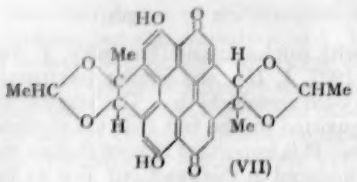

(VI)

acetaldehyde when heated with zinc chloride or with sulphuric acid (Favorsky, *J. Russian Phys. Chem. Soc.*, 1906, **38**, 741; *Chem. Zentr.*, 1907, I, 15), and similar treatment of a dioxolan structure such as that in (V) should also yield acetaldehyde. The suggestion that structures (V) or (VI) occur in erythroaphin is supported by the fact that the pigments do yield acetaldehyde when heated with zinc chloride. It is important to note that no volatile carbonyl compound other than acetaldehyde is produced in this reaction; this we take as strong evidence for the presence of $-O\cdot CH_2\cdot CH_2\cdot O-$ or $-O\cdot CHMe\cdot O-$ groupings.

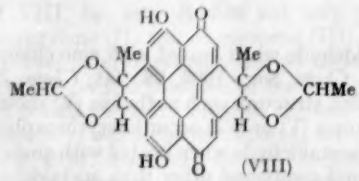
The yield of acetaldehyde obtained in the initial experiments with zinc chloride was low, as measured by the weight of dimedone derivative or of 2 : 4-dinitrophenylhydrazone isolated, but this was perhaps to be expected since much of the aldehyde liberated in presence of zinc chloride at high temperature would be expected to undergo a variety of transformations. It was nevertheless important to discover how much acetaldehyde could be obtained from the erythroaphins under milder conditions and we therefore turned our attention to the effect of sulphuric acid on the pigments. The erythroaphins are of course virtually insoluble in dilute sulphuric acid but dissolve readily enough in acid of 60% or higher concentration. Such solutions, even in concentrated sulphuric acid, do not appear to undergo any rapid change at room temperature but, on heating, acetaldehyde is evolved. The most favourable conditions for acetaldehyde production appear to be refluxing with 62% sulphuric acid, reaction appearing to be virtually complete in 12 hours. In a series of experiments it was established that under these conditions the amount of acetaldehyde obtained (as its 2 : 4-dinitrophenylhydrazone) from erythroaphin-*fb* was *ca.* 1·65 mols. and from erythroaphin-*sl* *ca.* 0·75 mol. From these results and those of model experiments on dioxan and benzodioxan, which similarly yield acetaldehyde under the same conditions, it may be concluded that erythroaphin-*fb* contains two separate groupings each capable of yielding 1 mol. of acetaldehyde. This, in turn, makes it highly probable that the molecule is symmetrical at least to the extent that there are two groups $C_5H_8O_2$ attached one to each side of the perylene system through the two central positions, and that these groups are of either type (V) or type (VI) [or conceivably one of type (V) and one of (VI)]. Even if it is assumed that the groupings yielding acetaldehyde are the source of 2 mols. of acetic acid in the Kuhn–Roth estimations, two additional *C*-Me groups must be present. These can only be located in angular positions as shown in (V) and (VI), and structures based on the assumption of two angular methyl groups on the alicyclic ring junction on one side of the perylene system and two hydrogen atoms on the other can be ruled out in view of the marked tendency of 13 : 14-dihydro-1 : 12-benzoperylene derivatives to lose two hydrogen atoms and become fully aromatic (cf. Clar, *Ber.*, 1932, **65**, 846).

As has already been mentioned, the erythroaphins-*fb* and -*sl* are undoubtedly stereoisomers and the fact that erythroaphin-*sl* yields only half as much acetaldehyde as the *fb*-isomer with sulphuric acid must have a stereochemical explanation. The production of 1 mol. of acetaldehyde from structure (VI) would presumably be due to an elimination reaction with subsequent formation of a vinyl ether which would then split yielding acetaldehyde. If the ring junction in (VI) were *cis*, then clearly the oxygen atom marked with an asterisk would be in the *trans*-position relative to the angular hydrogen atom and

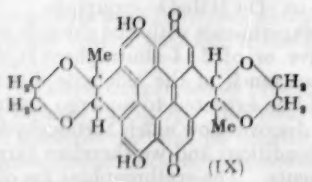
elimination should occur readily; with a *trans*-junction it would be in the *cis*-position and an elimination reaction would probably not occur. Similar arguments apply to structure (V), for, although it might be argued that acetaldehyde could be formed by hydrolysis, we do not consider that the reaction is one of simple hydrolysis of the erythroaphins; it is difficult to understand the remarkable difference in the yields of acetaldehyde obtained from the two isomeric pigments if the process is simply one of hydrolysis. If an initial elimination reaction is assumed, then stereochemical factors would in theory affect (V) in the same way as (VI). It therefore appears that four structures can be considered for the erythroaphins, *viz.*, (VII), (VIII), (IX), and (X), and that the difference between erythroaphin-*fb* and erythroaphin-*sl* is that in the former both the alicyclic rings are fused in the *cis*-position while in the latter one junction is *cis* and the other *trans*.



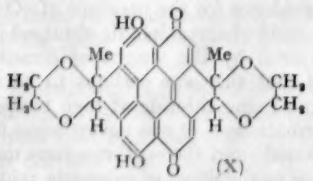
(VII)



(VIII)



(IX)



(X)

It is of interest that the production of acetic acid on pyrolysis of erythroaphin finds an explanation on any of these formulæ by invocation of a reaction analogous to that brought about by zinc chloride, and that the formation of small non-stoicheiometric amounts of silver iodide in Zeisel determinations carried out under very drastic conditions is also understandable. Another small point in agreement with these structures is that careful chromatographic study of the products of nitric acid oxidation of the erythroaphins failed to reveal the presence of any polybasic acids other than mellitic or oxalic acids, although succinic acid is completely stable to nitric acid under the reaction conditions employed.

The contrast between the production of twice as much acetaldehyde from erythroaphin-*fb* as from erythroaphin-*sl*, and the exactly similar yields (*ca.* 3·8 mols.) of acetic acid from both pigments in the Kuhn–Roth estimations calls for some comment. To explain this it is necessary to assume, on any formula, that the initial reaction under the Kuhn–Roth conditions (chromic acid in sulphuric acid) is oxidative attack by the chromic acid on the carbon atoms bearing methyl groups rather than an elimination reaction due to the acid; such an initial oxidation would, of course, remove stereochemical effects. As for as we are aware, no example of the production of acetic acid from $-O\cdot CH_2\cdot CH_2\cdot O-$ groupings in Kuhn–Roth estimations has been recorded in the literature, but it appears to us a reasonable assumption on the results of acid fission and pyrolysis of the erythroaphins. True, neither dioxan nor benzodioxan yields acetic acid under the conditions of the Kuhn–Roth estimation, but this does not necessarily invalidate our assumption since, in our view, the presence of an alkyl or other group in an angular position of a fused dioxan ring system would probably be essential for reaction to take the desired course.

We have as yet been unable to obtain decisive evidence of a positive nature for any one of these four formulæ, but various considerations lead us to believe that the choice can be narrowed down to two. Structures (VII) and (VIII) involve the presence in erythroaphin-*sl* of a dioxolan ring fused in the *trans*-position to a six-membered ring. Instances of *trans*-fused dioxolan rings are very rare (cf. *e.g.*, Angyal and Macdonald, *J.*, 1952, 686; Christian, Gogek, and Purvis, *Canad. J. Chem.*, 1951, **29**, 911); so much so, indeed, that

formation or non-formation of cyclic acetals is commonly regarded as satisfactory evidence of *cis*- or *trans*-orientation of hydroxyl groups in a cyclic 1 : 2-diol (*e.g.*, Angyal and Macdonald, *loc. cit.*). There is no doubt that structures (VII) and (VIII) would be under great strain if they contained a *trans*-junction and it is well-nigh impossible to build models of such structures using scale atomic models. Moreover, as will be shown in a later paper it is possible to convert a derivative of erythroaphin-*fb* into the corresponding one of erythroaphin-*sl* by irradiation in solution, and this *cis* → *trans* conversion is most improbable on the dioxolan formulæ (VII) and (VIII). For these reasons we feel that structures (VII) and (VIII) must be regarded as unlikely.

Structures (IX) and (X) present no such difficulty since there is no great difference between the stability of *cis*- and *trans*-fused dioxan systems and *fb*–*sl* interconversions are readily admissible. Taking into account all the facts and arguments so far presented, we feel justified in putting forward the view that the erythroaphin molecule is represented by structure (IX) or (X). The evidence so far presented does not permit of a decision between them. Such a decision can only be reached from a consideration of the stereochemical difference between erythroaphin-*fb* and erythroaphin-*sl* and the factors governing their interconversion.

Attempts to produce further degradative evidence of a positive nature to confirm or disprove structure (IX) or (X) have so far met with little success. Oxidative degradation of the pigments or their derivatives using a variety of reagents has led either to the production of hydroxylated erythroaphins or to complete disruption of the molecule, and no perylenecarboxylic acids have been obtained. Again, heating the erythroaphins with hydrogen bromide in acetic acid under various conditions has failed to yield ethylene dibromide; reaction occurs at temperatures above 160° with production of a black material insoluble in organic solvents but no volatile products seem to be formed. Ethylene dibromide is readily obtained under similar conditions from dioxan and benzodioxan, but this need not necessarily be significant since these compounds are not strictly analogous to the proposed erythroaphin structure. No compounds have as yet been described containing a dioxan ring fused to a second ring and bearing an angular methyl group; the presence of such a group might well have a profound effect on the ease of fission of one of the ether linkages. Other degradations depending on the fission of ether linkages which can be applied to dioxan itself have yielded no results of value with erythroaphin. The tetra-acetyldihydroerythroaphins do indeed form metal halide complexes, *e.g.*, with ferric chloride and aluminium bromide, just as dioxan does, but the formation of such complexes, although an argument in favour of ethereal oxygen atoms, is hardly specific to the dioxan system.

A more detailed examination of the infra-red spectra of the erythroaphins-*fb* and -*sl* (cf. Part V, *loc. cit.*) shows that they contain a number of features which are in accord with the structures (IX) and (X), especially in the light of the infra-red spectrum of dioxan (Malherbe and Bernstein, *J. Amer. Chem. Soc.*, 1952, **74**, 4408; Burket and Badger, *ibid.*, 1950, **72**, 4397). The erythroaphins, as mulls in hexachlorobutadiene, show absorption maxima ascribed to the aromatic CH group, CH_2, CH_3, and ether-oxygen (C–O–C) which are listed in the annexed Table. In addition several other bands, the origin of which is uncertain, are common to the spectra of the erythroaphins and dioxan, *e.g.*, at 1295—1285, 1266—1255, 1120—1111 and 1081—1074 cm.$^{-1}$, and the existence of these bands would also be consistent with the structures (IX) or (X).

Absorption maxima (cm.$^{-1}$).

	Erythroaphin-*fb*	Erythroaphin-*sl*	Dibenzoylerythroaphin-*sl*	Dioxan
Aromatic CH	3058	3040	*	—
	1481	1481	*	—
CH_2	2985	2950	2950	2967
	1456	1453	1449	1445
CH_3	2907	2899	2907	—
	1385	1383	1379	—
C–O–C	874 (864)	852	870	877

* Excluded because of presence of benzoyl groups.

Clearly further work will be necessary to establish conclusively the structure of the erythroaphins but we believe that, on the evidence available, (IX) and (X) give the most satisfactory representation and can at least be regarded as an adequate working hypothesis. When heated with sulphuric acid erythroaphin-*fb* yields in addition to acetaldehyde an almost black solid; this product might be expected, on the basis of (IX) and (X), to be a tetrahydroxydimethylcoronenequinone. Efforts to confirm or disprove this are in progress but are handicapped by the extreme insolubility of the material in solvents other than concentrated sulphuric acid, and by the poverty of existing knowledge of the chemistry of coronene derivatives. It may be mentioned, however, that the difficulty encountered in working with the much simpler **4** : 9-dihydroxy-**3** : 10-perylenequinone (Calderbank, Johnson, and Todd, *loc. cit.*) suggests that a coronene derivative of the type mentioned would be very intractable. The results of these experiments and of synthetic studies designed to produce structural analogues of the erythroaphins will be reported in due course.

Experimental

*Reaction of Erythroaphin-*sl *with Zinc Chloride.*—(i) Erythroaphin-*sl* (943 mg.) was intimately mixed with zinc chloride (20 g.) and placed in a small flask connected to a cooled (solid carbon dioxide) U-tube. The system was evacuated and the mixture heated at 300°/10^{-3} mm. for 45 min. The contents of the U-tube were washed with water into an aqueous solution of dimedone (250 c.c. of 0·3%) and kept for 2 days; then the crystalline precipitate (15 mg.) was separated, having m. p. 155° but not sharp. After recrystallisation from aqueous ethanol the product had m. p. 176°. A further quantity (28 mg.) of the product, m. p. 174°, was obtained from the original dimedone solution after it had been kept for 3 weeks. A sample of the dimedone derivative of acetaldehyde prepared in the same way had m. p. 139° (lit., 140°) but after 4 hours' heating under reflux in acetic acid the corresponding anhydride was obtained which had m. p. 175° (lit., 174°), not depressed on admixture with the specimen obtained from the degradation of erythroaphin-*sl* (Found, in a sample dried at 100° for 2 hr. at 10^{-3} mm.: C, 75·2; H, 8·2. Calc. for $C_{18}H_{24}O_6$: C, 75·0; H, 8·4%). The combined yield of acetaldehyde dimedone derivative (43 mg.) so obtained corresponds to 4% of the theoretical value for two mols. of acetaldehyde from one of erythroaphin-*sl*.

(ii) Erythroaphin-*fb* (1 g.) was mixed with zinc chloride (30 g.) and heated at 280°/10^{-3} mm. for 45 min. in a similar apparatus. The distillate was mixed with an ethanolic solution of 2 : 4-dinitrophenylhydrazine (10 c.c. of 0·1% solution containing 1% hydrochloric acid), warmed, and kept overnight; acetaldehyde 2 : 4-dinitrophenylhydrazone (24 mg., 0·015 mol.) was obtained as pale orange needles. This was separated but no more could be obtained from the filtrate. The acetaldehyde derivative was dissolved in benzene and chromatographed on a column of alumina (11 × 2·5 cm.), with benzene–ether (20 : 1) for the elution. Apart from a small brown band of impurity which remained at the top of the column, the product formed a single brownish-yellow zone; the eluate on evaporation and addition of ethanol gave the product (12 mg.) as light orange-yellow crystals, m. p. 158—160° (Found: C, 43·5; H, 3·5. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6%). A sample mixed with authentic acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 162—163°, had m. p. 161—162°, and in benzene formed one band on a column of alumina.

Reaction of the Erythroaphins with Sulphuric Acid.—Finely powdered erythroaphin-*sl* (50 mg.) was mixed with 62% sulphuric acid (15 c.c.) in a small flask fitted with condenser and gas inlet and outlet tubes. A slow stream of nitrogen was passed through the solution, and the exit gases from the top of the condenser were passed through four gas-absorption bottles in series, each containing cooled (<10°) 2 : 4-dinitrophenylhydrazine solution. The reaction mixture was heated at 120° for 12 hr., no further precipitate of acetaldehyde 2 : 4-dinitrophenylhydrazone being obtained thereafter. The precipitate was collected, washed and dried over phosphoric oxide at reduced pressure to constant weight (17 mg., 0·77 mol.). After crystallisation from ethanol the product was obtained as orange-yellow needles, identical with that obtained in the previous experiment.

A similar experiment with erythroaphin-*fb* (50 mg.) gave acetaldehyde 2 : 4-dinitrophenylhydrazone (36 mg., 1·65 mol.).

Metal Halide Complexes of Erythroaphin Derivatives.—(i) *Ferric chloride.* The addition of ferric chloride to tetra-acetyldihydroerythroaphin-*fb*, both in acetic anhydride solution, gave a purple-red solution, the visible spectrum of which resembled that of the original tetra-acetyl

compound except for a general displacement towards the red. Warming the solution led to a dark purple precipitate which was separated and dried. It had a green metallic appearance but was non-crystalline and insoluble in all the common solvents, including nitrobenzene. The complex in water decomposed to the original components and in concentrated sulphuric acid it gave a spectrum identical with that of erythroaphin (Part III, *loc. cit.*). No complex was obtained from 3 : 10-diacetoxyperylene and ferric chloride in acetic anhydride, even after 1½ hours' heating under reflux.

(ii) *Aluminium bromide.* Tetra-acetyldihydroerythroaphin-*fb* (166 mg.) was dissolved in dry benzene and a solution of anhydrous aluminium bromide (1·67 g.) in benzene (25 c.c.) was added. The precipitated orange-coloured complex was separated (centrifuge) quickly, suspended in fresh benzene (50 c.c.), and heated under reflux for 3 hr. The solution was poured into water (200 c.c.), and the mixture extracted repeatedly with benzene (6 × 200 c.c.). The combined benzene extracts were washed and dried and then chromatographed on silica (4 × 3 cm.), benzene–ether (100 : 8) being used to elute the product (40 mg.) which was crystallised first from benzene–ethanol and finally from chloroform–ethanol, to yield tetra-acetyldihydroerythroaphin-*fb* (18 mg.) (Found : C, 67·2; H, 4·7. Calc. for $C_{32}H_{32}O_{12}$: C, 67·1; H, 4·7%). The infra-red spectrum was identical with that of the authentic material. In another experiment the aluminium bromide complex was heated in benzene for 9 hr. but again the only product isolated was the original tetra-acetyl compound.

We thank the Royal Commission for the Exhibition of 1851 for a Senior Studentship (to B. R. B.), to the Department of Scientific and Industrial Research for a Senior Award (to J. R. Q.) to the University of Bombay for the Akbarnavis Scholarship (to B. S. J.), and to Imperial Chemical Industries Limited, Dyestuffs Division, for a grant (to A. C.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 23rd*, 1954.]

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*Studies in the Pyrolysis of Organic Bromides. Part I. The Kinetics of the Decomposition of Allyl Bromide.**

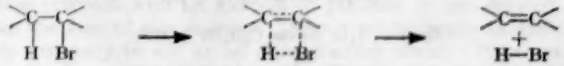
By ALLAN MACCOLL.

[Reprint Order No. 5766.]

The pyrolysis of allyl bromide in the temperature range 320—380° has been shown to be a homogeneous first-order process, involving an initial rupture of the C–Br bond. The rate constants are represented by the expression $k = 2{\cdot}11 \times 10^{13}\exp(-45{,}400/RT)$ (sec.$^{-1}$), the activation energy being in good agreement with the thermochemically determined C–Br bond dissociation energy (45·5 kcal. mole^{-1}). The overall reaction is, however, complex, and a reaction scheme has been suggested which explains the observed facts.

Introduction to a Series of Papers.

THE organic bromides, which decompose with the formation of hydrogen bromide and an olefin, form an interesting field for the study of the mechanism of gas-phase organic reactions. In all cases of saturated organic bromides examined previously, and to be described in the present series of papers, the stoicheiometry is well represented by the equation $C_nH_{2n+1}Br \longrightarrow C_nH_{2n} + HBr$, no appreciable side reaction being observed. *A priori*, two reasonable mechanisms can be envisaged. The first is a direct unimolecular splitting out of hydrogen bromide through a four-centre transition state as was indeed



discussed in connection with the pyrolysis of ethyl bromide (Vernon and Daniels, *J. Amer. Chem. Soc.*, 1933, **55**, 922; Fugassi and Daniels, *ibid.*, 1938, **60**, 771; Daniels and Veltman, *J. Chem. Phys.*, 1939, **7**, 756) and of *tert.*-butyl bromide (Kistiakowsky and Stauffer,

* A preliminary account of this work was given in *J. Chem. Phys.*, 1949, **17**, 1350.

J. Amer. Chem. Soc., 1937, **59**, 165). The second possibility is the initial breaking of a C–Br bond, previously considered by Daniels and Veltman (*loc. cit.*). These authors showed that, after the initial rupture, two courses were conceivable, the first leading to a radical non-chain mechanism; the second to a chain mechanism. The isolation and identification of examples of these processes form the subject of the present series of papers.

It may be that more than one type of mechanism is simultaneously concerned in the pyrolysis. Inhibition of radical-chain reactions has been achieved with nitric oxide (Staveley and Hinshelwood, *Nature*, 1936, **137**, 29) and with propene (Rice and Polly, *J. Chem. Phys.*, 1938, **6**, 273) through the interception of a chain-propagating radical by either of the following reaction steps:

$$R + NO \longrightarrow RNO$$

$$R + CH_3{\cdot}CH{:}CH_2 \longrightarrow CH_2\overset{\frown}{\text{—}}CH\text{—}CH_2 + RH$$

Thus it is to be expected that chain mechanisms involving bromine atoms would be eliminated by a reaction involving an attack on the propene molecule by a bromine atom:

$$Br + CH_3{\cdot}CH{:}CH_2 \longrightarrow CH_2\overset{\frown}{\text{—}}CH\text{—}CH_2 + RH$$

Szwarc (*J. Chem. Phys.*, 1948, **16**, 128; Szwarc, Ghosh, and Sehon, *ibid.*, 1950, **18**, 1142) has developed a flow method, with toluene both as carrier gas and as chain inhibitor, for studying the rate of breaking of a C–Br bond. The reaction scheme is

$$R\text{–}Br \longrightarrow R + Br$$

$$Br + C_7H_8 \longrightarrow C_7H_7 + HBr$$

$$2C_7H_7 \longrightarrow C_{14}H_{14}$$

This technique has been applied to benzyl and allyl bromides (Szwarc, Ghosh, and Sehon, *loc. cit.*) and to methyl bromide (Szwarc and Sehon, *ibid.*, 1950, **18**, 1685), but is limited to alkyl bromides without β-hydrogen atoms. The reason for this limitation will emerge later in this series. This view is supported by the work of Blades and Murphy (*J. Amer. Chem. Soc.*, 1952, **74**, 6219), who found negligible dibenzyl formation in the cases of ethyl, *n*-propyl, and *sec.*-propyl bromides. A fuller discussion of this point will be given in Part III which follows.

Although early work on the pyrolysis of bromides by Lessig (*J. Phys. Chem.*, 1932, **36**, 225), Vernon and Daniels (*loc. cit.*), and Fugassi and Daniels (*loc cit.*) was carried out in scrupulously clean reaction vessels, Daniels and Veltman (*loc. cit.*) and Kistiakowsky and Stauffer (*loc. cit.*) have shown the necessity of using vessels seasoned by contact with the reaction products in order to achieve reproducibility. All the work to be described in the present series was done in seasoned vessels. A further important factor noted by all the previous workers in this field is the marked catalytic effect of oxygen upon the pyrolysis. For this reason it is important that all traces of oxygen be removed from the reaction system.

Some possible mechanisms involving an initial splitting of a C–Br bond have been discussed by Daniels and Veltman (*loc. cit.*) in the case of ethyl bromide. The first is a non-chain radical mechanism

$$C_2H_5Br \xrightarrow{k_1} C_2H_5 + Br$$

$$Br + C_2H_5Br \xrightarrow{k_2} C_2H_4Br + HBr$$

$$C_2H_4Br + C_2H_5 \xrightarrow{k_3} C_2H_4 + C_2H_5Br$$

For such a mechanism, the overall rate constant equals that for the initial step. Recent estimates of the bond dissociation energy of C–Br in ethyl bromide, ~67 kcal. mole^{-1}, enable this mechanism to be eliminated in view of the magnitude of the observed activation

energy (53 kcal. mole^{-1}). A second mechanism involves chain propagation through the unstable bromoethyl radical: $C_2H_4Br \xrightarrow{k_3} C_2H_4 + Br$, instead of the third step in the foregoing scheme. If, for example, the chain-termination step is

$$C_2H_4Br + Br \xrightarrow{k_4} \text{end of chain}$$

the overall reaction will be of first order and the rate constant given by $k = (k_1k_2k_3/k_4)^{\frac{1}{2}}$, so that the activation energy, $E = \frac{1}{2}(E_1 + E_2 + E_3 - E_4)$ could be much less than that required to break the C–Br bond.

Evidence that chains may play a part in the pyrolysis of ethyl bromide was obtained by a study of the photolysis and pyrolysis of ethyl bromide–acetaldehyde (Roof and Daniels, *J. Amer. Chem. Soc.*, 1940, **62**, 2912; Roof, *ibid.*, 1944, **66**, 358). These reactions were studied at a temperature where ethyl bromide decomposes only slowly and acetaldehyde is quite stable. The thermal decomposition of the mixture was explained in terms of reaction chains initiated in the acetaldehyde by the radicals formed in the ethyl bromide decomposition. The photolysis could be interpreted as a photosensitisation of the ethyl bromide decomposition, which in turn started chains in the acetaldehyde.

The pyrolysis of methyl bromide has been studied by Meissner and Schumaker (*Z. physikal. Chem.*, 1940, *A*, **185**, 435). The reaction was homogeneous and resulted in the formation of carbon, hydrogen bromide, and methane, the last two substances in the approximate ratio of 2 : 1. The ratio of final to initial pressure was about 1·4. The kinetics of the reaction were complex, retardation by the products being observed. On this evidence, Whittingham (*Discuss. Faraday Soc.*, 1947, **2**, 175) advanced the following mechanism:

$$CH_3Br \longrightarrow CH_3 + HBr$$
$$CH_3 + CH_3 \longrightarrow CH_4 + C$$

The possibility of a chain mechanism cannot, however, on the evidence be ruled out.

The object of the present series of papers is to investigate the mechanism of pyrolysis of organic bromides, and in particular to isolate and study the unimolecular process. Two questions arise. (i) How do the parameters of the rate expression for unimolecular decomposition vary with alteration in structure? (ii) How does the rate of unimolecular decomposition vary in a homologous series?

Experimental

Apparatus and Experimental Technique.—The experiments were carried out by using a metal-bath thermostat, bismuth solder being used as the bath fluid. The bath consisted of a cylindrical metal pot of diameter 12″ and depth 12″ to which was attached a flange. To the flange was bolted a circular metal plate carrying eight wells sealed at the bottom to hold the reaction vessels. The top also supported a stirrer bearing and contained a number of holes for the introduction of a thermoregulator and of thermocouples. The outside of the pot was covered with asbestos paper and wound with resistance wire. The bath was mounted on bricks and surrounded with a cylindrical jacket, the intervening space being packed with asbestos wool. This gave about 6″ of insulating material in all directions. Temperature control was obtained to about ±025° by a combination of energy regulator and bimetallic thermoregulator. No horizontal temperature gradient could be detected in any of the wells, but there was a vertical gradient of about 0·5°. Temperatures were measured with a nichrome–eureka thermocouple, which had been calibrated by the National Physical Laboratory and was considered to be accurate within ±0·5°.

Since the reaction proceeds with an increase in pressure, it was decided to measure the rate by determining the rate of this increase. Also since hydrogen bromide is produced in the reaction, it was necessary to use an all-glass reaction vessel. Pressures were measured by means of a glass diaphragm gauge shown in Fig. 1. This is a modified form of that used by Karrer, Wulf, and Johnston (*J. Ind. Eng. Chem.*, 1922, **14**, 1015). The diaphragm *A* is made by blowing a thin bulb and then flattening the end in a flame. To the tube is sealed a frame *B* to which are attached two platinum wires *C* and *D*. The former, in the shape of a V, rests firmly against the diaphragm, so as to follow its movements; *D* may be adjusted

through the seal *E*, so as just to make contact with C. The diaphragm is then mounted in the tube *F* and the wires sealed into the mercury cups *G*. To facilitate the sealing, the platinum wires were first welded to nickel and then to tungsten. When the pressure is the same on each side of the diaphragm the wires are adjusted so as just to make contact. A small pressure on the upper side suffices to break the contact as indicated by the inclusion of a torch bulb and battery in the external circuit. This gauge zero, the excess pressure required to break the contact, can be subtracted from all subsequent pressure readings to give the actual pressure on the lower side of the diaphragm. The diaphragm gauge was used as a null instrument, pressures being read on a mercury manometer. The accuracy was within $\pm 0{\cdot}5$ mm.

The vacuum system is shown in Fig. 2. The reaction vessel *A* was cylindrical, of about 250 c.c. capacity, and to it was attached the diaphragm gauge *B*. A side-arm *C* was connected to the vessel by capillary tubing so as to minimise dead space. The side-arm and connecting tubing were wound with nichrome wire through which a current was passed to prevent condensation. The reaction system was isolated from the remainder of the apparatus by the vacuum tap *D*, lubricated with Silicone grease. A liquid-air trap *G*, which could be isolated from the rest of the system by means of taps *E* and *F*, was used for condensing out the products

FIG. 1. *The diaphragm gauge.*

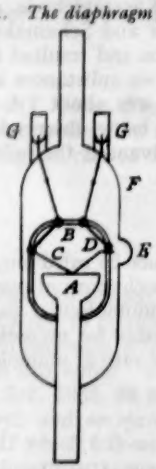
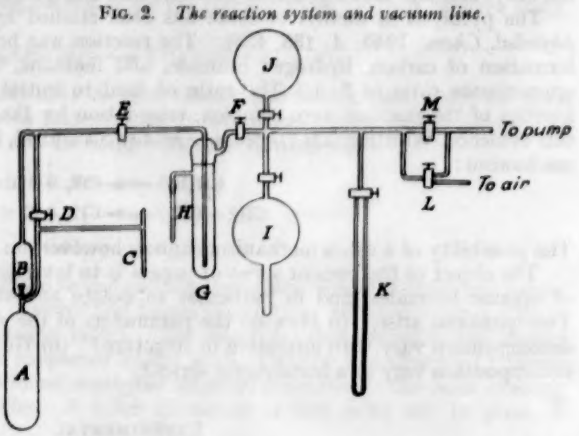


FIG. 2. *The reaction system and vacuum line.*



at the end of a run. The removable side-arm *H* facilitated their removal from the system. To the vacuum line were attached two 5-l. flasks *I* and *J*, which could be used for gas storage. One of these had a narrow tube sealed on the bottom to permit condensation of non-permanent gases. The manometer *K* and a by-pass capillary two-way tap *L*, which allowed a fine adjustment of the pressures, completed the vacuum line. The apparatus was evacuated by a two-stage rotary oil pump, the large-bore tap *M* being used for rapid pumping. As it was found that the vibration of the pump tended to make the pressure readings somewhat erratic, during a run an exhausted 5-l. flask was used as a vacuum reservoir.

At the commencement of a run, a small phial filled with previously degassed allyl bromide was introduced into the side-arm *C*. This was then cooled in liquid air, and the top sealed off. The system was then evacuated to about 10^{-4} mm., and the reaction vessel isolated by closing the tap *D*. The gauge zero was then determined. By heating *C*, the allyl bromide was rapidly distilled into the reaction vessel, and the pressure measured as a function of time. At the end of a run the system was carefully exhausted, trap *G* surrounded with liquid air, and the tap *F* closed. Opening *C* caused the products to distil into *G*. Tap *E* was then closed and the products were distilled into *H*, from which they could be removed. Between runs the vacuum system was thoroughly exhausted. In order to ascertain whether the sealing-off technique affected the reaction an alternative method of introducing the allyl bromide was tried. It consisted of instantaneously connecting a hot reservoir containing allyl bromide vapour to the reaction system. By varying the temperature of the reservoir different pressures of allyl bromide could be introduced. There was no detectable difference between the runs initiated in this way and those carried out in the manner described previously.

In the case of runs in the presence of added gases, the technique was slightly different. With the permanent gases, the allyl bromide was introduced in the normal manner, the apparatus exhausted, and the gauge zero measured. The gas was then admitted to the system from the reservoir, and excess removed by pumping. The pressure could then be read on the manometer, or in the case of low pressure on a McLeod gauge. Tap *D* was then closed, and the reaction started. In the case of propene, indentations were made in the side-arm *C* about ½" from the bottom. After the apparatus was exhausted, propene was admitted, tap *D* shut, and the propene in the reaction vessel condensed out with liquid air. The propene remaining in the vacuum system was then taken back to the reservoir. The gauge zero was then determined, and the propene distilled into the reaction vessel from *C*. The propene pressure was then measured. The propene was then condensed out again in *C*, collecting in the bottom, and the top of *C* blown off. The phial of allyl bromide was then introduced, the side-arm sealed off, and the apparatus exhausted. The run was then started in the normal fashion. The indentations in the side-arm *C* prevented the relatively "hot" phial of allyl bromide from coming in contact with the condensed propene. An alternative technique was to introduce the allyl bromide in the usual manner into *C*, cool it with liquid air, and exhaust the vessel. The liquid air was then replaced by carbon dioxide–ether and finally a freezing mixture. Propene was then admitted to the system, and the pressure measured. The run could then be commenced as usual. In the case of bromine, the former procedure was followed.

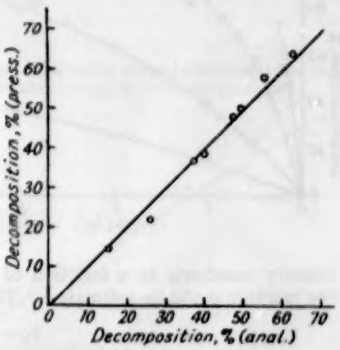


FIG. 3. *The percentage decomposition as determined from pressure measurements plotted against that determined by analysis of the hydrogen bromide produced.*

As a check on the rate constants obtained from the pressure–time curves, an alternative procedure involving the determination of the hydrogen bromide evolved from a given weight of allyl bromide was employed. A reaction vessel fitted with a side-arm was joined to the vacuum line. Into the side-arm was placed a phial containing a weighed amount of allyl bromide. This was then distilled into the reaction vessel, outgassed by successive evaporation and freezing, and the reaction vessel sealed off. Six vessels were introduced into the thermostat, which had had its temperature raised by about 2° to allow for the cooling effect of the vessels, and were then removed after given intervals of time, their tips were broken under standard alkali, and the hydrogen bromide was estimated.

The allyl bromide used in these experiments was obtained by drying a commercial sample (over P_2O_5) and fractionally distilling it through a 3′ column packed with glass helices. A distillate of constant b. p. and refractive index was collected, *viz.*, b. p. 69·8°/760 mm., n_D^{20} 1·4692. The most recent literature values are b. p. 69·9°/760 mm., n_D^{20} 1·4693 (Kharasch and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 2468).

The Nature and Order of the Reaction.—From a study of the pressure–time curves, it was found that the ratio of the final to initial pressure approached 1·5, an observation best explained on the basis of an overall reaction of the type $C_3H_5Br \longrightarrow \frac{1}{2}(C_6H_8) + HBr$. If $(p_0 - p)$ is the pressure of allyl bromide at time *t*, the pressures of C_6H_8 and HBr are respectively $\frac{1}{2}p$ and p. If the total pressure at time *t* is *P*, then

$$P = p_0 - p + \tfrac{1}{2}p + p = p_0 + \tfrac{1}{2}p.$$

The percentage decomposed (*D*) is thus given by $D = 100p/p_0 = 200(P - p_0)/p_0$. Again, the percentage undecomposed may be calculated from the hydrogen bromide produced. In Fig. 3 the percentage decomposed, calculated from the mean of about six pressure runs, is plotted

against the percentage decomposed as determined by the analytical experiments. The points all lie close to the straight line of unit slope, passing through the origin, thus justifying the use of pressure–time curves in determining the rate of decomposition.

The order of the reaction was established by plotting the logarithm of the percentage undecomposed against time. For both the pressure and the analytical experiments, good straight lines were obtained up to about 60% decomposition. Further, as is shown in the following Table, the rate constants obtained by the two methods are in essential agreement.

Temp.	10^4k_1 (sec.$^{-1}$) (pressure)	10^4k_1 (sec.$^{-1}$) (analytical)
320°	3·89	3·96
340	13·7	14·0

Each entry in the table is the mean of five runs. The reaction is thus of the first order.

The homogeneity of the reaction was established by packing reaction vessels with glass tubing so as to give surface-volume ratios of approximately 1, 2, and 3. By plotting the

FIG. 4. *The percentage decomposition at four temperatures as a function of time.* I, 380°; II, 360°; III, 340°; IV, 320°.

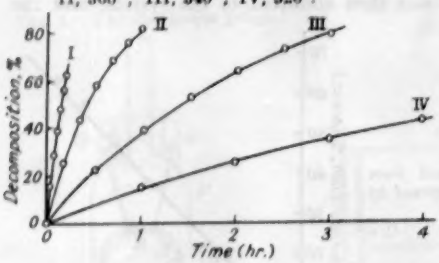
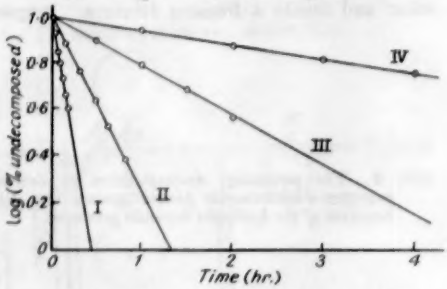


FIG. 5. *The logarithm of the percentage decomposition at four temperatures as a function of time.* Temperatures as for Fig. 4.



velocity constants as a function of S/V, and extrapolating to $S/V = 0$, the homogeneity of the reaction could be estimated. The results are shown below, the runs being done at 320°:

	p_0 = 210 mm.				p_0 = 470 mm.			
S/V (cm.$^{-1}$)	0	1·2	2·1	3·0	0	1·2	2·1	3·0
10^4k_1 (sec.$^{-1}$)	(3·10)	3·26	3·44	3·79	(3·82)	3·86	3·92	4·06

As the surface-volume ratio of the reaction vessel used for the pressure runs was ~1 cm.$^{-1}$, it can be estimated that the reaction is about 95% homogeneous at 200 mm. and 99% homogeneous at 500 mm. During the reaction, a carbonaceous deposit developed on the walls of the vessel. As the pressure runs were done in seasoned vessels, it was of interest to see if the constants determined for cleaned and for seasoned vessels differed: the respective values of k_1 were $3{\cdot}89 \times 10^{-4}$ and $3{\cdot}86 \times 10^{-4}$ sec.$^{-1}$, so the wall coating has no appreciable effect on the rate. It may thus be concluded that the reaction is predominantly homogeneous.

To test the completeness of the reaction, with respect to elimination of hydrogen bromide, sealed tubes (P_0 ~900 mm.) were left in the thermostat for 60 hr. at 320°. The mean decomposition was 85%.

Attempts to isolate the C_6H_8 hydrocarbon at the end of a run were not successful. As the kinetic apparatus was only capable of handling small quantities of allyl bromide, product runs were done in a 5-l. reaction vessel. The liquid reaction products were condensed out after a run and fractionated through a small column. Evidence was obtained for the presence of three substances in small quantities. The first fraction had b. p. 58—59°, n_D^{20} 1·4402 (Found: C, 30·7; H, 4·6; Br, 65·0%), and can reasonably be regarded as a mixture of 1-bromopropene (b. p. 60°; n_D^{20} 1·4554. Calc.: C, 29·8; H, 4·1; Br, 66·1%) and *iso*propyl bromide (b. p. 59·4°; n_D^{20} 1·4228. Calc.: C, 29·3; H, 5·7; Br, 65·0%). The last fraction, which boiled at about 80°, had n_D^{23} 1·4908 (Found: C, 84·9; H, 7·7; Br, 7·5%). Thus complete separation from bromo-compounds was not attained. However, a measurement of the absorption spectrum showed that the fraction was largely benzene.*

* The author is indebted to Dr. E. M. F. Roe and Dr. R. N. Beale, of the Royal Cancer Hospital, for this measurement.

Results.—The results of the pressure experiments are shown in the following Table. The initial pressures were obtained by extrapolation to zero time, and the velocity constants obtained from the slope of the log (% undecomposed)–time curves. The mean percentage decomposition–time curves are shown in Fig. 4, and the logarithmic plots in Fig. 5. The data shown

T =	320°		340°		360°		380°	
p_0 (mm.)	10^5k (sec.$^{-1}$)	p_0 (mm.)	10^5k (sec.$^{-1}$)	p_0 (mm.)	10^5k (sec.$^{-1}$)	p_0 (mm.)	10^5k (sec.$^{-1}$)
460	4·03	670	13·5	510	47·7	490	136
430	3·97	474	13·8	494	45·8	400	132
398	3·87	420	13·8	445	45·3	400	130
367	3·88	410	13·9	432	46·0	362	132
344	3·95	331	13·7	338	46·5		
				312	47·5		

above were fitted to the Arrhenius equation $k = 2{\cdot}11 \times 10^{13} \exp(-45{,}400/RT)$ (sec.$^{-1}$), the Arrhenius plot being shown in Fig. 6.

A number of experiments were done at pressures below 300 mm., in order to investigate the effect of pressure on the velocity constant. As the velocity constant at low pressures depends rather critically upon the extrapolated initial pressure, the accuracy of these results

FIG. 6. *The Arrhenius plot.*

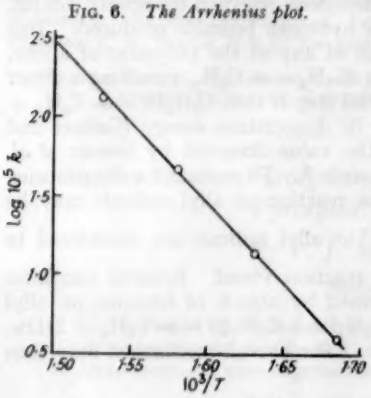
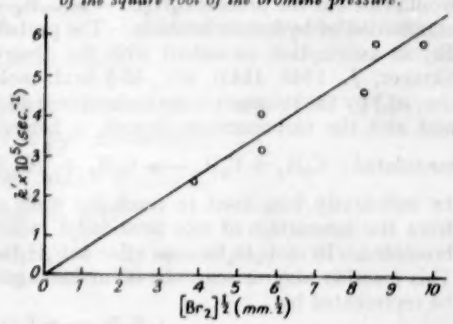


FIG. 7. *The initial rate of decomposition as a function of the square root of the bromine pressure.*



does not warrant an exhaustive analysis of them, so it suffices to say that a fall in velocity constant is observed for pressures <300 mm.

As oxygen has been reported to have marked effects upon the pyrolysis of ethyl and the propyl bromides, runs were carried out at 320° with oxygen pressures of 0·9 and 10 mm. The initial allyl bromide pressures were 294 and 378 mm., respectively, and so the velocity constants in the absence of oxygen would be $3{\cdot}79 \times 10^{-5}$ and $3{\cdot}94 \times 10^{-5}$ sec.$^{-1}$, respectively. The observed velocity constants were $3{\cdot}75 \times 10^{-5}$ and $3{\cdot}99 \times 10^{-5}$ sec.$^{-1}$, indicating that oxygen at small partial pressures has no effect on the reaction.

The fall in rate constant as the initial pressure of bromide decreases has already been referred to. It was originally interpreted as the fall in rate constant predicted by Lindemann's theory. The effect of added nitrogen and hydrogen upon the rate constant was thus investigated, and it appeared that, whereas nitrogen has no effect upon the rate, hydrogen is capable of restoring the low-pressure rate to its limiting value. It should be emphasized that in view of the chemical complexity of the overall reaction, to be discussed in the next section, it is now considered unlikely that the fall in the rate constant and its restoration by hydrogen can be interpreted in terms of a Lindemann mechanism.

The effect of bromine on the rate of decomposition was investigated. An increase in the rate was observed, but because of the possibility of altered stoicheiometry of the reaction only the initial fractional rate of pressure increase was derived from the results. This quantity $(1/P_0)(dP/dt)_0 = k'$ is shown as a function of the square root of the bromine pressure in Fig. 7. It is seen that a linear relation exists. The bromine was observed to disappear from the reaction system fairly rapidly, and for this reason the initial rates were employed.

The reaction was studied in the presence of varying amounts of propene,* the results being shown in the following Table, where p_i is the partial pressure of propene. It is seen that the

	T = 380°						
p_i (mm.)	0	43	124	129	0	82	177
p_0 (mm.)	400	410	385	390	306	303	275
10^4k (sec.$^{-1}$)	132	127	127	132	115	116	124

rate is independent of the propene pressure. This observation rules out the possibility of long bromine atom chains being concerned in the decomposition.

Discussion of Results

It has been shown that the gas-phase pyrolysis of allyl bromide in the temperature range 320—380° is a homogeneous, first-order process. In calculating the rate constants from the pressure–time curves, the equation $C_3H_5Br \longrightarrow \frac{1}{2}(C_6H_8) + HBr$ was employed. This was consistent with the observed pressure change, and the percentage decomposition calculated on this basis agreed with that derived from direct titration of the hydrogen bromide produced. The products observed were hydrogen bromide, benzene, and a carbonaceous coating. A product which would not have been detected by the technique used in the present investigation was propene. This has been observed by Szwarc, Ghosh, and Sehon (*loc. cit.*) to the extent of 20—30% of the hydrogen bromide produced. This last observation, together with the complete absence of any of the polymers of allene, would rule out the process $C_3H_5Br \longrightarrow C_3H_4 + HBr$, $2C_3H_4 \longrightarrow C_6H_8$, involving a direct elimination of hydrogen bromide. The probable initial step is thus $C_3H_5Br \longrightarrow C_3H_5 + Br$, an assumption consistent with the observed C–Br dissociation energy (Gellner and Skinner, *J.*, 1949, 1145), *viz.*, 45·5 kcal. mole^{-1}. The value observed by Szwarc *et al.* (*loc. cit.*) by the toluene-carrier technique is 47·5 kcal. mole^{-1}. To account for the propene, and also the carbonaceous deposit, a heterogeneous reaction of allyl radicals may be postulated: $C_3H_5 + C_3H_5 \longrightarrow C_3H_6 + \frac{1}{x}(C_{3x}H_{4x})$. The allyl radicals are considered to be sufficiently long-lived to reach the walls of the reaction vessel. Benzene can arise from the interaction of two bromoallyl radicals formed by attack of bromine on allyl bromide: $Br + C_3H_5Br \longrightarrow HBr + C_3H_4Br$; $C_3H_4Br + C_3H_4Br \longrightarrow C_6H_6 + 2HBr$. This reaction may or may not occur homogeneously. The overall mechanism may then be represented by

$$C_3H_5Br \longrightarrow C_3H_5 + Br$$
$$Br + C_3H_5Br \longrightarrow C_3H_4Br + HBr$$
$$C_3H_5 \longrightarrow \tfrac{1}{2}C_3H_6 + \frac{1}{2x}(C_{3x}H_{4x}) \quad \text{(surface)}$$
$$C_3H_4Br \longrightarrow \tfrac{1}{2}C_6H_6 + HBr$$

and the overall reaction by

$$C_3H_5Br \longrightarrow HBr + \tfrac{1}{4}C_3H_6 + \tfrac{1}{4}C_6H_6 + \frac{1}{4x}(C_{3x}H_{4x})$$

It remains to account for the 1-bromopropene and the *iso*propyl bromide found in the products. These may be regarded as the result of side reactions. The former could arise from

$$C_3H_5Br + CHBr\overset{\frown}{—}CH—CH_2 \longrightarrow CHBr{:}CH{\cdot}CH_3 + C_3H_4Br$$

and, being a substituted vinyl bromide, would be expected to be stable in the temperature range considered. The *iso*propyl bromide, on the other hand, would result from a normal addition of hydrogen bromide to propene.

The decrease in rate constant with decreasing initial pressure of allyl bromide, and the restitution of the rate with hydrogen, might be taken as indicative of the decrease in rate constant with decreasing pressure predicted by Lindemann's theory of unimolecular reactions. However, recent calculations by Slater (*Phil. Trans.*, 1953, **246**, 57) suggest

* The author is indebted to Imperial Chemical Industries Limited, Billingham Division, for a gift of propene.

that the observed pressure range is far too high to account for the falling off in this manner. As a more probable alternative it is suggested that, as the pressure falls, one of the steps subsequent to the initial breaking of the C–Br bond may become slow. The effect of hydrogen could then be explained by its chemical intervention.

Additional confirmation of the non-chain character of the reaction comes from the observed lack of inhibition of the reaction by propene. Again, this reaction is unique in comparison with other bromides studied, in that oxygen has no effect upon the rate. This would suggest the impossibility of initiating chains in allyl bromide, and can be interpreted in terms of the stability of the bromoallyl radical with respect to a splitting off of a bromine atom:

$$CH_2\overset{\frown}{-}CH\overset{\frown}{-}CHBr \longrightarrow CH_2{\cdot}CH{\cdot}CH + Br$$

Confirmation of the presence of bromine atoms in decomposing allyl bromide comes from an unpublished observation by P. J. Thomas that the presence of decomposing allyl bromide accelerates the decomposition of certain other organic bromides. It may reasonably be concluded that allyl bromide decomposes by a bromine atom non-chain mechanism.

The author acknowledges an award of an Imperial Chemical Industries Research Fellowship and a grant for the purchase of apparatus from the Central Research Fund by the University of London. He also thanks Dr. T. Iredale for stimulating his interest in these matters, and Professor C. K. Ingold, F.R.S., for many helpful discussions.

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Studies in the Pyrolysis of Organic Bromides. Part II. The Pyrolysis of* n-*Propyl Bromide.*†

By P. J. Agius and Allan Maccoll.

[Reprint Order No. 5767.]

n-Propyl bromide decomposes into propene and hydrogen bromide in the temperature range 300—380°, according to a rate equation of order 1·5. The rate constants were expressible as

$$k_{1\cdot5} = 7{\cdot}24 \times 10^{10} \exp(-33{,}800/RT) \text{ (mole}^{-\frac{1}{2}} \text{ c.c.}^{\frac{1}{2}} \text{ sec.}^{-1})$$

A great increase in the surface : volume ratio had only a relatively small effect upon the rate. Propene, on the other hand, strongly inhibited the reaction. It is concluded that the reaction is homogeneous and that the mechanism is of a chain type, the initiating step being the breaking of a carbon–bromine bond.

The first work reported on the pyrolysis of the propyl bromides was by Aronstein (*Rec. Trav. chim.*, 1882, **1**, 134), who showed that both *n*- and *iso*-propyl bromide decompose at high temperatures to yield propene and hydrogen bromide. Nef (*Annalen*, 1901, **318**, 14) showed that when *n*-propyl bromide was passed through a pumice-filled tube at 500°, practically the calculated yield of propene was produced. Lessig (*J. Phys. Chem.*, 1932, **36**, 2325) verified that the reaction in the case of the propyl bromides was $C_3H_7Br \rightarrow C_3H_6 + HBr$, the propene being identified both by absorption in bromine water and by combustion. First-order rate coefficients calculated from the rate of pressure increase in clean vessels on the basis of the above reaction were found to increase markedly with increasing initial pressure. The reaction was shown to be homogeneous, and oxygen had a strongly catalytic effect. No activation energy was reported. However, on the basis of some unpublished results, Daniels and Veltman (*J. Chem. Phys.*, 1939, **7**, 756) quote an activation energy of 36 kcal.

* Part I, preceding paper.
† A preliminary account of this work was given in *J. Chem. Phys.*, 1950, **18**, 158.

Experimental Methods and Results

A commercial sample of *n*-propyl bromide was distilled through a 1-m. column packed with glass helices. The middle fractions, of constant b. p. and refractive index, were collected. The sample used for the kinetic study had b. p. 71·15° (71·00°), n_D^{25} 1·4318 (1·4318), d_4^{25} 1·3431 (1·3431), the values in parentheses being due to Timmermans ("Physical Constants of Pure Organic Compounds," Elsevier, Netherlands, 1950).

For the inhibition experiments, propene was prepared by dehydration of *iso*propyl alcohol with phosphoric oxide; it was purified by several trap-to-trap distillations through a tube containing phosphoric oxide supported on granular calcium chloride. Finally, the propene was distilled into a glass storage reservoir and thoroughly out-gassed.

The apparatus and the technique used were essentially as described in Part I, except that an aluminium block thermostat was used in place of the metal bath. Temperature control to ±0·25° was obtained, the temperatures being measured with a calibrated nichrome–eureka thermocouple.

In order to verify the stoicheiometry of the reaction, analytical runs were carried out in sealed tubes, the hydrogen bromide being determined by titration, and the propene by an

Fig. 1.

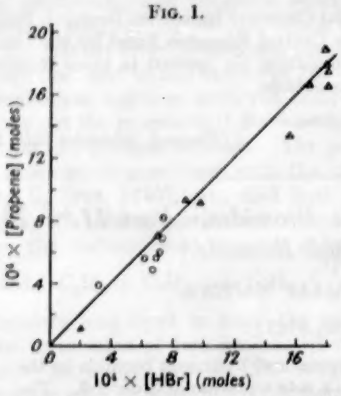

Fig. 2.

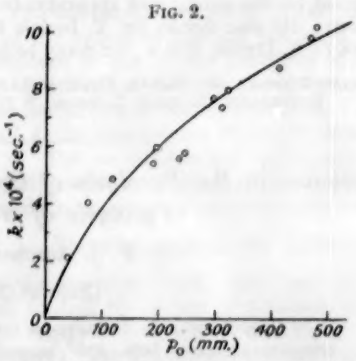

Fig. 1. *The equivalence of propene and hydrogen bromide produced in the pyrolysis of* n*-propyl bromide.*

Δ, Mean initial pressure 609 mm.; ○, mean initial pressure 256 mm. The straight line is of unit slope.

Fig. 2. *First-order rate coefficients as a function of initial pressure.*

estimation of the residual volume of undissolved gas. A plot of the moles of hydrogen bromide against moles of propene produced is shown in Fig. 1, the results being obtained at two different initial pressures, ~250 and ~600 mm. In view of the inaccuracy inherent in the method of estimating the propene, the agreement is quite good.

The completeness of the reaction was tested by taking infinity measurements both of the hydrogen bromide produced and of the total pressure. Thus after *ca.* 24 hr., the mean extents of decomposition were 81·9% starting from an initial pressure of 600 mm., and 91·0% starting from 250 mm. The percentage decompositions derived from pressure measurements are shown in Table 1. The results show conclusively that an equilibrium exists, since the higher the initial

Table 1.

p_0 (mm.)	373	282	193	114	333	161	37·4
T	300°	300°	340°	340°	360°	360°	360°
p_∞/p_0	1·73	1·76	1·85	1·89	1·78	1·82	1·87
Decompn., %	73	76	85	89	78	82	87

pressure at any given temperature, the lower the percentage decomposition. The quantitative nature of the results is however doubtful, inasmuch as the equilibrium is not a simple one, the C_3H_7Br being either *n*- or *iso*-propyl bromide. Again, in the pressure runs, dead-space errors play some part and so the percentage decompositions recorded are lower limits. Qualitatively,

at least, the observations are in favour of the equilibrium $C_3H_7Br \rightleftharpoons C_3H_6 + HBr$, and since only the early stages of the reaction have been used in calculating the kinetic constants, the complex nature of the reverse reaction may be neglected.

It has been mentioned that Lessig found the first-order constants for the pyrolysis of *n*-propyl bromide to be markedly dependent on pressure; this could be a normal Lindemann decrease in a unimolecular mechanism, or could be due to the reaction's being of a higher order. In order to settle this matter, the pressure variation of the rate was measured at 360° over a range 40—500 mm. The first-order rate constant as a function of pressure is shown in Fig. 2. It will be seen that there is no tendency to approach a limiting value as the initial pressure is increased, as would be expected for a Lindemann decrease. The results thus suggested a reaction

FIG. 3.

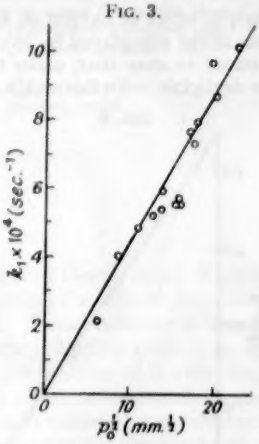

FIG. 4.

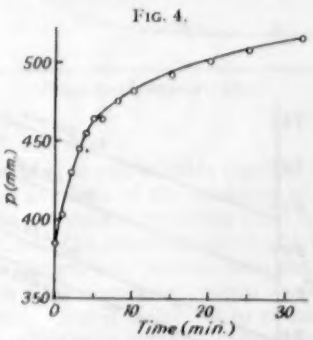

FIG. 3. *The relation between the first-order rate coefficients and the square root of the initial pressure*

FIG. 4. *The effect of oxygen on the pressure–time curve.*

of a higher order, and so the first-order constants were plotted against the square root of the initial pressure. A good straight line, passing through the origin, shown in Fig. 3, resulted. This was suggestive of the reaction's being of order 1·5 and so rate constants of this order were calculated which, while showing a scatter about the mean value, showed no significant trend with initial pressure. Their behaviour is to be compared with that of the first-order coefficients, which varied from $2{\cdot}13 \times 10^{-4}$ sec.$^{-1}$ to $10{\cdot}2 \times 10^{-4}$ sec.$^{-1}$ in the pressure range 40—500 mm. Similar independence of initial pressure of the constants of order 1·5 was observed at other temperatures, so it was concluded that the reaction was of this order.

Further to verify this, two analytical experiments using the sealed-tube technique, were done at 320°, each involving about a dozen analytical determinations of hydrogen bromide. The percentage decomposition as measured by the hydrogen bromide produced and interpolated from a smooth curve is shown in Table 2. These results lead to values of $k_{1.5}$ of $31{\cdot}6 \times 10^{-3}$

TABLE 2.

Time (min.)	0	12	24	36	48	60
		$p_0 \sim 610$ mm.				
Decompn., %	0	16·8	30·0	38·2	45·5	51·7
		$p_0 \sim 260$ mm.				
Decompn., %	0	7·8	16·1	24·2	31·5	37·2

and $28{\cdot}6 \times 10^{-3}$ mole$^{-\frac{1}{2}}$ c.c.$^{\frac{1}{2}}$ sec.$^{-1}$, respectively, in fair agreement with the mean value obtained from pressure measurements, namely, $32{\cdot}7 \times 10^{-3}$ mole$^{-\frac{1}{2}}$ c.c.$^{\frac{1}{2}}$ sec.$^{-1}$. The first-order coefficients in the two cases are respectively $2{\cdot}26 \times 10^{-4}$ and $1{\cdot}34 \times 10^{-4}$ sec.$^{-1}$.

The pressure measurements were done in well-seasoned vessels. As seasoning by the products of reaction is rather slow, it was decided to use the observation (Part I, *loc. cit.*) that pyrolysis of allyl bromide produced a heavy carbonaceous coating on the walls of the vessel, so seasoning

of the reaction vessel was effected by this means. Rate measurements on the pyrolysis of *n*-propyl bromide done in vessels thus seasoned were reproducible and consistent. In order to check the homogeneity of the reaction, a number of runs were done in a vessel whose surface : volume ratio had been increased by a factor of 17 over that of the unpacked vessel. The rate constants obtained at two temperatures are shown in Table 3, where the values for the

TABLE 3.

Temp.	$10^3k_{1\cdot5}$ (packed)	$10^3k_{1\cdot5}$ (unpacked)	Temp.	$10^3k_{1\cdot5}$ (packed)	$10^3k_{1\cdot5}$ (unpacked)
320°	22·0	32·7	360°	166	144

unpacked vessel are also shown. In view of the very large increase in surface : volume ratio, the observed change in rate is very small.

Lessig (*loc. cit.*) had already commented upon the catalytic effect of oxygen on the decomposition of *n*-propyl bromide. Although the interpretation of the rôle played by oxygen in the pyrolysis of alkyl bromides is difficult, it was deemed necessary to show that, under the experimental conditions used in the present work, its effects were negligible. To this end, a number of

FIG. 5.

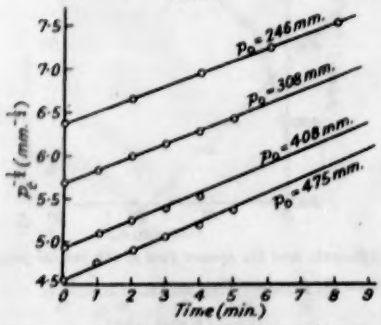

FIG. 6.

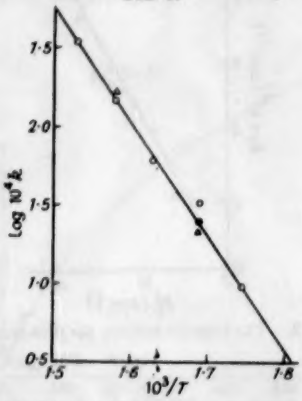

FIG. 5. *The 1·5-order plots at* 360°.

FIG. 6. *The Arrhenius plot.* ○, Vessel unpacked, seasoned. △, Vessel packed, seasoned. ●, Vessel unpacked, unseasoned.

TABLE 4.

Temp.	300°	320°	340°	360°	380°
No. of runs	6	8	10	15	5
$10^3k_{1\cdot5}$ (mole$^{-\frac{1}{2}}$ c.c.$^{\frac{1}{2}}$ sec.$^{-1}$)	9·54	32·7	61·4	147	346

runs were done in the presence of varying small pressures of oxygen (2—0·02 mm.). A characteristic pressure–time curve is shown in Fig. 4. An interesting feature of the curves is the abrupt change in slope, suggesting that the oxygen was used up after a certain time. This was borne out by the fact that the greater the pressure of oxygen, the greater the percentage decomposition of the bromide before the discontinuity in the slope occurs. It was also shown that when the oxygen pressure was ~0·02 mm. the effect had become very small, and so it is safe to regard the oxygen effect as being absent in the normal runs, as the vessel was always evacuated to less than 0·001 mm.

The results of the pressure investigations at different temperatures are shown in Table 4. In Fig. 5 are shown some of the 1·5-order plots (reciprocal square root of bromide pressure at time t, against time). The results were fitted to the Arrhenius equation $k_{1\cdot5} = 7{\cdot}24 \times 10^{10} \exp(-33{,}800/\boldsymbol{RT})$ mole$^{-\frac{1}{2}}$ c.c.$^{\frac{1}{2}}$ sec.$^{-1}$, the resulting plot being shown in Fig. 6.

In view of the order of the reaction, which strongly suggests a chain mechanism, the inhibiting power of propene was investigated. Because of the large partial pressures of propene required to produce maximum inhibition, it was not found possible accurately to ascertain the order of the reaction under these conditions,* so, to show the effect of increasing partial pressure

* Dr. P. J. Thomas has since shown the maximally inhibited rate to be that of a first-order reaction. Further evidence indicates that it is indeed the unimolecular splitting out of hydrogen bromide.

of propene, the values of $k_{1\cdot5}$ at 360° are plotted against the partial pressure of propene in Fig. 7. Points are shown for both packed and unpacked vessels, and the approach of the rate to a limiting value is clearly illustrated. It is noteworthy that the ratio of final to initial pressure became greatly reduced, a fact which bears out the view expressed earlier of an equilibrium between propyl bromide and its decomposition products.

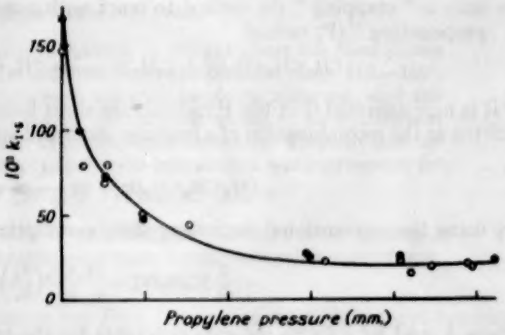

FIG. 7. *1·5-Order rate coefficients in the presence of added propylene, showing the approach to a limiting value as the propylene pressure is increased.*
○, Unpacked vessel;
●, packed vessel.

DISCUSSION

The observed kinetic order of the decomposition of *n*-propyl bromide together with the marked inhibitory effect of propene are conclusive evidence of the existence of a chain mechanism. This conclusion is strengthened by the presence of relatively short and quite irreproducible induction periods in some of the runs. The relatively small effect on the rates of decomposition of a very large increase in the surface : volume ratio means that the reaction either is essentially homogeneous or is a heterogeneous process in which the chains are both initiated and terminated at a surface. But it is difficult to visualise such a process leading to the observed 1·5-order kinetics. The most probable explanation of the results is a homogeneous chain mechanism.

In considering the various chain mechanisms possible for *n*-propyl bromide, the obvious chain-initiation and chain-propagating steps are

$$CH_3{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{k_1} CH_3{\cdot}CH_2{\cdot}CH_2 + Br$$

$$Br + CH_3{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{k_2} CH_3{\cdot}CH{\cdot}CH_2Br + HBr$$

$$CH_3{\cdot}CH{\cdot}CH_2Br \xrightarrow{k_3} CH_3{\cdot}CH{:}CH_2 + Br$$

The fate of the *n*-propyl radical is of little importance in view of the great length of the chains (see p. 978). If, on the one hand, the *n*-propyl radicals decompose on reaching the walls of the reaction vessel, the products of this reaction would be below the limits of observation. If, on the other hand, they entered into the hydrogen-abstraction reaction

$$CH_3{\cdot}CH_2{\cdot}CH_2 + CH_3{\cdot}CH_2{\cdot}CH_2Br \longrightarrow CH_3{\cdot}CH_2{\cdot}CH_3 + CH_3{\cdot}CH{\cdot}CH_2Br$$

the effect would be to introduce a factor of 2 into the overall rate expression. Once again, the propane produced would be below the limit of observation. Conceivable chain-ending steps are

$$Br + Br + X \xrightarrow{k_6} Br_2 + X$$

$$Br + CH_3{\cdot}CH{\cdot}CH_2Br \xrightarrow{k_7} \text{end of chain}$$

Application of the usual stationary-state approximation shows that reaction (7) would lead to first-order kinetics and so may be excluded. To the same approximation, if it is assumed that X may be either C_3H_7Br or C_3H_6, then (4) leads to the observed 1·5 order with respect to *n*-propyl bromide at a given initial pressure, but the initial fractional rate is found to be independent of *n*-propyl bromide pressure, so this scheme can also be rejected.

A possible interpretation of the kinetics lies in a further analysis of the attack of a bromine atom on a *n*-propyl bromide molecule (P. J. Thomas, Thesis, University of London, 1953). If the attack is at a β-hydrogen atom, then the resultant radical may undergo dissociation as shown in (3). However, if the attack is at the α- or γ-position the radical may be assumed to be stable as regards C–Br bond breaking. It is, however, possible for such a " stopping " (S) radical to react with a *n*-propyl bromide molecule to produce a " propagating " (P) radical

$$CH_3{\cdot}CH_2{\cdot}CH_2Br + C_3H_7Br \xrightarrow{k_5} CH_3{\cdot}CH{\cdot}CH_2Br + C_3H_7Br \quad . \quad . \quad . \quad . \quad (6)$$

If it is now assumed that the P radicals are short lived, then the chain-ending step may be written as the recombination of a bromine atom and an S radical :

$$CH_3{\cdot}CH_2{\cdot}CH_2Br + Br \xrightarrow{k_6} \text{end of chain} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

By using the conventional stationary-state assumption, the overall rate may be written as

$$-\frac{d}{dt}[C_3H_7Br] = \left\{\frac{k_1k_2k_5}{k_6}\left(\frac{k_2}{k_2'}\right)\right\}^{\frac{1}{2}}[C_3H_7Br]^{\frac{3}{2}}$$

where k_2 and k_2' refer to the rate constants for the production of P and S radicals by the attack of a bromine atom on a *n*-propyl bromide molecule. No precise values are available for the activation energies of the individual reactions, so it is difficult to estimate the overall activation energy. It is, however, obvious that it would be much less than the C–Br bond dissociation energy. Further experiments are being carried out by Dr. P. J. Thomas in order more firmly to establish the mechanism.

The inhibition produced by added propene may be explained by assuming (8) to be in

$$Br + CH_3{\cdot}CH{:}CH_2 \longrightarrow HBr + CH_2{-}H{-}CH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

competition with (2) and (2′). At maximal inhibition, the chain component of the reaction would be reduced to

$$C_3H_7Br \longrightarrow C_3H_7 + Br$$
$$Br + C_3H_6 \longrightarrow C_3H_5 + HBr$$

which would be unobservable in the temperature range concerned, in view of the magnitude of the C–Br bond dissociation energy. This view has been confirmed by the independent studies of the maximally inhibited reaction by Thomas using *cyclo*hexene (to be published later in this series) in a static system, and by Blades and Murphy using a toluene carrier-gas technique (*J. Amer. Chem. Soc.*, 1952, **74**, 6219).

An estimate may be made of the chain length in the decomposition by using a value of the C–Br bond dissociation energy, suggested by Linnett *et al.* (*Proc. Roy. Soc.*, 1952, **216**, *A*, 361) of 67·9 kcal. Assuming a value of 10^{13} for the pre-exponential factor in the Arrhenius equation, we have $k_1 = 10^{13}\exp(-67{,}900/\boldsymbol{R}T)$. The chain length γ is thus

$$\gamma = 7{\cdot}24 \times 10^{-3}c^{\frac{1}{2}}\exp(+34{,}100/\boldsymbol{R}T)$$

where c is the concentration in mole c.c.$^{-1}$. This gives at 600° K and 300 mm. initial pressure, a chain length of the order of 10^7.

One of us (P. J. A.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Grant, and the other (A. M.) to the University of London for an Imperial Chemical Industries Research Fellowship, during the tenure of which this work was completed. Both authors acknowledge the encouragement given by Professor C. K. Ingold, F.R.S., and the many discussions one of them has had with Dr. P. J. Thomas.

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University College, London, W.C.1. [*Received, September 29th*, 1954.]

Studies in the Pyrolysis of Organic Bromides. Part III. The Pyrolysis of* iso*Propyl Bromide.*†

By Allan Maccoll and P. J. Thomas.

[Reprint Order No. 5768.]

The decomposition of *iso*propyl bromide in the gas phase has been shown to be a homogeneous, first-order reaction in the temperature range 310—350°. Propene and hydrogen bromide were the only products observed, and the first-order constants decreased during the reaction owing to an equilibrium between the products and the undecomposed bromide. Propene had no effect on the rate, the variation of which with temperature was represented by

$$k = 4{\cdot}17 \times 10^{13} \exp(-47{,}800/RT)(\text{sec.}^{-1})$$

The results are consistent with a unimolecular elimination of hydrogen bromide. The rate constants maintained their normal values down to 25 mm. initial pressure of the bromide.

Early qualitative studies (for references see Part II) showed that the propyl bromides decomposed at high temperatures into propene and hydrogen bromide. The first attempt to study the kinetics of the pyrolysis of *iso*propyl bromide was made by Lessig (*J. Phys. Chem.*, 1932, **36**, 2335). The reaction was carried out in scrupulously cleaned vessels, but the results were not very satisfactory owing to a lack of reproducibility. It was concluded that the reaction was of the first order, although the rate coefficients showed a marked dependence upon the initial pressure of *iso*propyl bromide. Thus at 346·5°, the first-order rate coefficients were in the range 2—6 $\times 10^{-3}$ sec.$^{-1}$. It was also observed that the ratio of the final to the initial pressure was less than 2, as demanded by the equation $C_3H_7Br \longrightarrow C_3H_6 + HBr$.

Experimental

A commercial sample of *iso*propyl bromide was twice distilled through a 1-m. column packed with glass helices. It then had b. p. 59·32°/760 mm. (59·32°), n_D^{18} 1·4285 (1·42847), the values in parentheses being those of Timmermans and Martin (*J. Chim. phys.*, 1929, **25**, 423). During the work comparisons of the behaviour of the sample used immediately after purification were made with a sample that had been stored for several months and again after the same sample has been dried ($CaCl_2$) and redistilled. Further, samples from different sources were compared. In no case was there any evidence that the nature of the sample had any effect on the reaction rate.

Propene, for the inhibition studies, was prepared as in Part II (*loc. cit.*).

The apparatus and technique used were in essence the same as those described in Part I (*loc. cit.*). The rate of decomposition was measured by observing the rate of pressure increase, after having demonstrated that the percentage decomposition obtained from pressure measurements agreed with that calculated from the hydrobromic acid present, as determined by titration. Fig. 1 shows that the agreement between these two methods is very good. These observations imply that the reaction is well represented by $C_3H_7Br \longrightarrow C_3H_6 + HBr$, and that side reactions are present, if at all, only to a negligible extent. Further evidence comes from the fact that the products of reaction were completely and rapidly absorbed by bromine water, and were completely condensable in liquid air. These observations show that no saturated light hydrocarbons or hydrogen is formed during the reaction.

It was found that traces of oxygen exerted a powerful catalytic effect on the decomposition, and so it was essential not to allow oxygen to enter the reaction vessel. This was achieved by filling the reaction system between runs with oxygen-free nitrogen, which had been washed by bubbling through Fieser's solution to remove the last traces of oxygen. Nitrogen thus treated was examined in a mass spectrometer and no trace of oxygen was found.‡ The following Table shows the type of irreproducibility that was encountered before the nitrogen-flushing technique was developed. The rate coefficients, referring to 324°, are of first order, for reasons that will

* Parts I and II, preceding papers.

† A preliminary account of this work appeared in *J. Chem. Phys.*, 1951, **19**, 977.

‡ The authors are indebted to Dr. C. A. Bunton for this test.

appear later. These are to be compared with the average value of $1{\cdot}00 \times 10^{-4}$ sec.$^{-1}$ obtained for the non-catalysed reaction.

p_0 (mm.)	212	250	238	218	164	285
10^4k_1 (sec.$^{-1}$)	2·80	2·89	5·37	3·76	6·44	6·67

The reaction was also catalysed by clean Pyrex surfaces, but as has been reported in other studies of the pyrolysis of organic halides, the gradual decomposition of the reaction products deposits a fine carbonaceous film which effectively eliminates the catalytic action. In the present reaction, the formation of an effective coating by this method took a considerable time. In a series of experiments starting with a clean reaction vessel, the rate constants showed a gradual decrease to a constant value when the wall effect had been effectively eliminated by the carbon coating.

As has been shown in Part I, the pyrolysis of allyl bromide leads to a relatively heavy carbonaceous coating on the walls of the vessel, so the reaction vessels were seasoned efficiently and rapidly by utilising this fact (see Part II, p. 975). Further, a reaction vessel which had

FIG. 1.

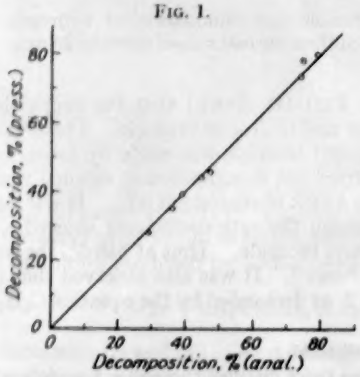


FIG. 2.

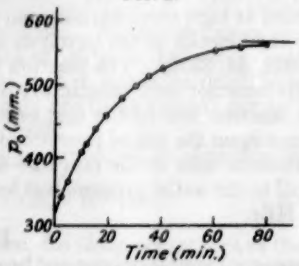


FIG. 1. *The percentage decomposition calculated from measurements of total pressure as a function of the percentage decomposition determined analytically.*

FIG. 2. *The variation of the total pressure of decomposing isopropyl bromide with time.*

been coated by prolonged contact with propene and hydrogen bromide, and which gave reproducible rate constants, was treated with allyl bromide; the reaction rates remained unaltered, and hence the coating produced by allyl bromide had no direct effect on the seasoned rate. In the following Table, which relates to $T = 341°$, the rate constants for a number of different

Surface of vessel	Clean	Seasoned by products	Seasoned by allyl bromide
10^4k_1	15·3, 14·9	4·16, 4·17	4·00, 4·30

conditions of seasoning are shown. If air or oxygen was admitted into the vessel between runs, the coating was removed by oxidation.

The order of the reaction was shown to be unity by working in seasoned vessels in the absence of oxygen. Fig. 2 shows a typical pressure–time curve, and Fig. 3, curve (*a*), a typical log plot. It will be noted in Fig. 2 that the pressure increase is only about 90% of that to be expected. The interpretation of this in terms of an equilibrium will be discussed later. Again in Fig. 3, it will be seen that the first-order plot departs from linearity after about 30% reaction. This may also be interpreted in terms of an equilibrium between *iso*propyl bromide and propene and hydrogen bromide. For this reason, only the initial reaction rate has been determined.

In order to test the homogeneity of the reaction, a series of runs were done in a vessel, the surface : volume ratio of which had been increased by a factor of three over that of the unpacked vessel. The packed vessel was seasoned with allyl bromide. The results obtained are shown below. It may be concluded that the reaction is essentially homogeneous.

Temp.	10^4k_1, sec.$^{-1}$ (packed)	10^4k_1, sec.$^{-1}$ (unpacked)	k_1 packed/ k_1 unpacked	Temp.	10^4k_1, sec.$^{-1}$ (packed)	10^4k_1, sec.$^{-1}$ (unpacked)	k_1 packed/ k_1 unpacked
320°	1·00	1·00	1·00	335°	3·24	2·79	1·16
330	2·05	1·95	1·05	345	5·52	5·19	1·06
335	3·01	2·79	1·08	345	5·39	5·19	1·04

Kinetic Results.—The velocity constants obtained in the pressure range 200—450 mm. and temperature range 310—350° are set out below. As it was not convenient always to work at a given temperature, the velocity constants corrected to some convenient temperature within the range by means of the Arrhenius equation are shown. The results may be represented

Temp.	312°	319°	329°	341°	347°
No. of runs	5	3	8	8	4
10^5k_1, sec.$^{-1}$	5·92	9·56	18·0	40·4	58·3

by the Arrhenius equation

$$k = 4{\cdot}17 \times 10^{13} \exp(-47{,}800/RT)(\text{sec.}^{-1})$$

and the plot of log k against T^{-1} is shown in Fig. 4.

FIG. 3.

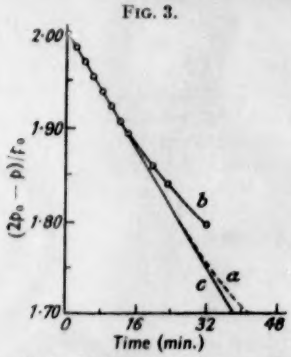


FIG. 4.

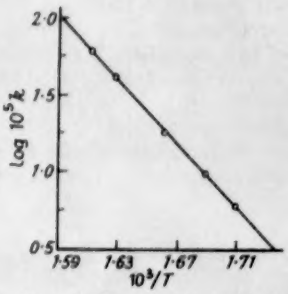


FIG. 3. *The effect of added propene upon the falling away from the first-order law*: (a) *in the absence of propene*, (b) *in the presence of* 240 *mm. of propene*, (c) *theoretical first-order plot in the absence of reverse reaction.*

FIG. 4. *The Arrhenius plot.*

To test further the invariance of the rate constant with pressure, the pressure range 30—120 mm. was covered, the results being shown below, where k_1 is in sec.$^{-1}$. The values of k_1 have been corrected to 327°. The low-pressure value, $1{\cdot}58 \times 10^{-4}$ sec.$^{-1}$ is to be compared with the

Temp.	p_0 (mm.)	10^4k_1	$(10^4k_1)_{corr.}$	Temp.	p_0 (mm.)	10^4k_1	$(10^4k_1)_{corr.}$
326·5°	116	1·48	1·55	329·5°	28·5	1·69	1·53
327·5	72	1·79	1·76	328·5	27·5	1·66	1·55
328·5	42·5	1·62	1·52				Mean 1·58

value obtained from the Arrhenius equation, namely, $1{\cdot}62 \times 10^{-4}$ sec.$^{-1}$. The good agreement is to some extent fortuitous, since the experimental error tends to be greater at lower initial pressures. It can be concluded that there is no evidence for any decrease in the rate down to 30 mm.

A number of runs were done in the presence of about 250 mm. of added propene (p_i). The velocity constants are shown below, k_1 being in sec.$^{-1}$. The mean values at 327° and 335° are to be compared with the values obtained from the Arrhenius equation, namely, $1{\cdot}64 \times 10^{-4}$ and $2{\cdot}79 \times 10^{-4}$ (sec.$^{-1}$). The reaction is thus clearly not affected by the presence of propene.

	$T_c = 327°$					$T_c = 335°$			
Temp.	p_0 (mm.)	p_i (mm.)	10^4k_1	$(10^4k_1)_{corr.}$	Temp.	p_0 (mm.)	p_i (mm.)	10^4k_1	$(10^4k_1)_{corr.}$
327°	248	241	1·62	1·62	335°	244	252	2·81	2·81
328	283	237	1·77	1·66	336	246	244	2·96	2·88
327·5	242	233	1·72	1·67					Mean 2·84
			Mean	1·65					

Fig. 3 illustrates the earlier fall-off in the first-order plot for a run carried out in the presence of propene.

Experiments done in the presence of added bromine showed no very marked increase in the rate. Thus with about 2% of bromine, the initial fractional rate of pressure increase was about 30% greater than in the absence of bromine. Further, after 20% reaction there was no visible trace of bromine in the condensed contents of the reaction system.

Since allyl bromide had been used for seasoning the reaction vessel, it was thought desirable to determine the rate in the presence of a small amount of allyl bromide, but no alteration of the rate constant was observed.

Discussion

The pyrolysis of *iso*propyl bromide in a seasoned vessel has been shown to be a homogeneous first-order reaction yielding propene and hydrogen bromide. The rate constants are very reproducible, the same results having been recorded with different samples of material and over an extended period of time. In the pressure range studied, 25—450 mm., there is no evidence for a decrease in the rate constants. However, the first-order constants fall during the course of a run and this phenomenon is accentuated in the presence of added propene. Further, the initial rate constants are the same in the presence of propene.

The fall in the first-order constants during the course of a run, the fact that the ratio of final to initial pressure is less than 2 and the enhanced fall-off in the constants in the presence of propene can all be explained in terms of an equilibrium $C_3H_7Br \rightleftharpoons C_3H_6 + HBr$ lying well to the right. This equilibrium has not been investigated in detail because of the difficulty of correcting for dead space in the apparatus and because the equilibrium must be complex as C_3H_7Br represents either *n*- or *iso*-propyl bromide. Further evidence for the equilibrium is afforded by the lack of evidence for side reactions.

Three possible mechanisms exist for the decompositions of *iso*propyl bromide. In the first place the initial step may be the breaking of the C–Br bond

$$C_3H_7\text{–}Br \longrightarrow C_3H_7 + Br$$

followed by a non-chain radical mechanism such as has been postulated by Daniels for ethyl bromide or by one of us for allyl bromide. Such a mechanism might be

$$C_3H_7Br \longrightarrow C_3H_7 + Br$$
$$Br + C_3H_7Br \longrightarrow HBr + C_3H_6Br$$
$$C_3H_6Br + C_3H_7 \longrightarrow C_3H_6Br + C_3H_6$$

in which case the overall activation energy of the process would be the C–Br bond dissociation energy. As this is most certainly greater than 47·8 kcal. this mechanism can be dismissed.

The second possible mechanism by analogy with *n*-propyl bromide is the Br chain reaction. To fit the first-order law, a mechanism somewhat different from that for *n*-propyl bromide must be considered; a possibility is

$$C_3H_7Br \xrightarrow{k_1} C_3H_7 + Br$$
$$Br + C_3H_7Br \xrightarrow{k_2} C_3H_6Br + HBr$$
$$C_3H_6Br \xrightarrow{k_3} C_3H_6 + Br$$
$$Br + C_3H_6Br \xrightarrow{k_7} \text{end of chain}$$

This would lead to the overall rate constant $k = (k_1k_2k_3/k_7)^{\frac{1}{2}}$ and activation energy $E = \frac{1}{2}(E_1 + E_2 + E_3 - E_7)$. Such a mechanism should be powerfully inhibited by propene by competition between (2) and

$$Br + C_3H_6 \longrightarrow HBr + C_3H_5$$

No such inhibition is observed.

The remaining possibility is the direct unimolecular split through a four-centre transition state

$$CH_3\text{—}\underset{\displaystyle Br}{CH}\text{—}CH_3 \longrightarrow CH_3\text{—}\underset{\displaystyle Br\cdots H}{CH}\text{=}CH_2 \longrightarrow CH_3\text{—}CH\text{=}CH_2 \quad (Br^{+}\text{—}H^{-})$$

Such a process is consistent with all the known facts. It would explain the clean nature of the reaction and the inability of propene to inhibit it. No satisfactory *a priori* estimation can be made of the activation energy for such a process: all that can be said is that the value 47·8 kcal. is not unreasonable. Such a mechanism has in fact been postulated by Kistiakowsky and Stauffer (*J. Amer. Chem. Soc.*, 1937, **59**, 165) for the decomposition of *tert.*-butyl bromide.

It might be argued that the catalytic effect of oxygen is evidence against the suggested mechanism. This is quite marked, as is shown in Fig. 5, which gives the pressure–time curves for a normal run and for one in the presence of about 0·1 mm. of oxygen. It does seem possible, however, that the oxygen effect produces long chains which may effectively swamp the normal elimination of hydrogen bromide. To test this view, the reaction was carried out in the presence of a trace of oxygen and added propene. The oxygen effect appeared at first to be inhibited, but then the rate of reaction slowly increased, giving rise to a sigmoid-type pressure–time curve. The catalysis produced by oxygen is far too marked to be merely due to oxidation of the carbonaceous film, thus exposing a clean surface. No extensive investigation of the oxygen effect has been attempted in the present work.

An interesting outcome of this work is the marked difference of mechanism in the pyrolysis of *n*- and *iso*-propyl bromide. In Part II it was shown that *n*-propyl bromide decomposes by a chain mechanism in which the initiation and propagation steps are:

$$n\text{-}C_3H_7Br \longrightarrow C_3H_7 + Br$$
$$Br + C_3H_7Br \longrightarrow HBr + C_3H_6Br$$
$$C_3H_6Br \longrightarrow C_3H_6 + Br$$

*iso*Propyl bromide on the other hand decomposes by the direct splitting out of hydrogen bromide. The difference in behaviour in these two cases can be explained by a more detailed examination of the steps in the chain mechanism postulated in Part II.

$$C_3H_7Br \xrightarrow{k_1} C_3H_7 + Br$$
$$Br + CH_2{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{k_2} CH_2{\cdot}CH{\cdot}CH_2{\cdot}Br + HBr$$
$$\xrightarrow{k_2'} CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}Br + HBr$$
$$CH_2{\cdot}CH{\cdot}CH_2Br \xrightarrow{k_3} CH_2{:}CH{\cdot}CH_2 + Br$$
$$CH_2{\cdot}CH_2{\cdot}CH_2Br + C_3H_7Br \xrightarrow{k_4} CH_2{\cdot}CH{\cdot}CH_2Br + C_3H_7Br$$
$$CH_2{\cdot}CH_2{\cdot}CH_2Br + Br \xrightarrow{k_5} Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Br$$

The reaction of order 1·5 can be explained in terms of the facile decomposition of propagating (P) radicals ($CH_2{\cdot}CH{\cdot}CH_2Br$) and the condition $8k'_2k_4[C_3H_7Br] \gg k_1k_5$. This condition is readily seen to be satisfied at ordinary pressures. In the case of *n*-propyl bromide the initial Br-atom attack to give a P radical is on a secondary hydrogen atom whereas that to give a stopping radical is on a primary hydrogen atom hence $k_2^N > k_2'^N$ *. Also the radical-exchange reaction will be facilitated by the replacement of a secondary C–H bond by a primary one. However, with *iso*propyl bromide $k_2'^S > k_2^S$, and also $k_4^S \ll k_4^N$. Further, as will be seen later, $k_3^S \ll k_3^N$ and so all factors are in favour of a chain mechanism for *n*-propyl bromide. Finally, the unimolecular rate for *iso*propyl bromide is about 200 times greater than for *n*-propyl bromide (Green, Harden, Thomas, and Maccoll, *J. Chem. Phys.*, 1953, **21**, 178), which would further tend to favour the unimolecular mechanism.

Estimates of the C–Br bond dissociation energies in *n*- and *iso*-propyl bromides have recently been given by Linnett (*Proc. Roy. Soc.*, 1952, **216**, *A*, 361) as 67·9 and 67·6 kcal., respectively. On the assumption, which will also underlie subsequent arguments, that the pre-exponential terms in the expression for the rate constants of analogous steps are not greatly different, these values would imply $k_1^N \sim k_1^S$.

Van Artsdalen *et al.* (*J. Chem. Phys.*, 1944, **12**, 479; 1954, **22**, 28) have observed the

* The superscripts N and S refer to *n*- and *iso*-propyl bromide, respectively.

rate of bromine-atom attack on primary and tertiary C–H bonds. The reported activation energies are

$$Br + C_3H_8 = C_3H_7 + HBr;\ E = 13{\cdot}3 \text{ kcal.}$$
$$Br + iso\text{-}C_4H_{10} = C_4H_9 + HBr;\ E = 11{\cdot}4 \text{ kcal.}$$

These values would suggest that for *n*- and *iso*-propyl bromide

$$E_2^N - E_2'^N \sim 1 \text{ kcal.};\ E_2'^S - E_2^S \sim 1 \text{ kcal.}$$

At the relevant temperature, the 1 kcal. difference in activation energy would lead to a factor of about 3 in the rate.

FIG. 5.

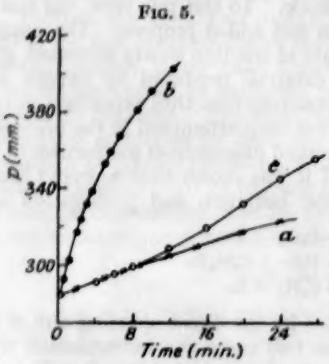


FIG. 6.

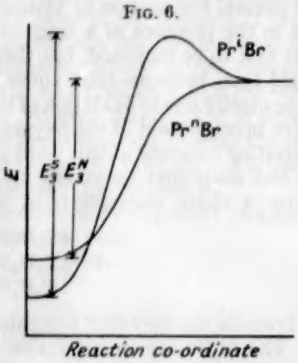


FIG. 5. *The rate of decomposition of* iso*propyl bromide* (a) *in the absence of oxygen,* (b) *in the presence of* ~0·1 *mm. of oxygen, and* (c) *in the presence of* ~0·1 *mm. oxygen and* 120 *mm. of propene.*

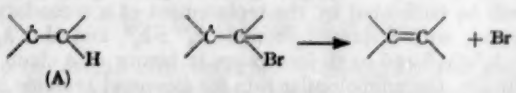
FIG. 6. *The activation energies for bromoalkyl-radical decomposition.*

Information relating to the radical-exchange reaction comes from the work of Trotman-Dickenson and Steacie, reported by the former author (*Discuss. Faraday Soc.*, 1951, **10**, 112). The activation energies for methyl-radical attack upon primary and secondary C–H bonds are respectively 10·2 and 8·2 kcal. This would suggest that $k_4^N \sim 10k_4^S$ in the temperature range experimentally investigated.

An estimate of the stability of the bromoalkyl radical can be obtained by thermochemical arguments analogous to those used by Szwarc (*ibid.*, p. 144) in his discussions of the C–H bond dissociation energies in radicals of the type (A). He used the equation

$$D(\text{M–H}) = \Delta H_f(\text{H}) + \Delta H_f(\text{M}) - \Delta H_f(\text{M–H})$$

where M–H represents the radical formed by the addition of a hydrogen atom to the olefin M and ΔH_f(A) is the enthalpy of formation of A. Provided ΔH_f(Br–M) can be estimated, a lower limit for the activation energy of the reaction



(A)

can be obtained by this method. The enthalpies of formation of the bromoalkyl radicals can be obtained by use of the equation

$$\Delta H_f(\text{M–Br}) = D(\text{Br–M–H}) + \Delta H_f(\text{Br–M–H}) - \Delta H_f(\text{H})$$

if it is assumed that the C–H bond dissociation energy is the same in the alkyl bromide (Br–M–H) as in the unsubstituted hydrocarbon. The values used for D(C–H) are taken from the work of Stevenson as quoted by Evans (*ibid.*, p. 1) and are 97 kcal. for a primary C–H bond and 94 for a secondary. From the known values of the enthalpies of formation of *n*- and *iso*-propyl bromide, −18·7 and −23·8 kcal., respectively (Mortimer, Pritchard,

and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220), the values 23·3 and 21·2 kcal. can be calculated for the ΔH_f of $CH_3{\cdot}\dot{C}H{\cdot}CH_2Br$ and $CH_3{\cdot}CHBr{\cdot}\dot{C}H_2$, respectively. Applying now the equation

$$D(\text{M–Br}) = \Delta H_f(\text{Br}) + \Delta H_f(\text{M}) - \Delta H_f(\text{M–Br})$$

and using the value 4·9 kcal. for ΔH_f(propene) (Selected Values of the Properties of Hydrocarbons, Nat. Bureau of Standards, Washington) we find the M–Br bond dissociation energies for the above two radicals to be 8·3 and 10·4 kcal., respectively. In order to estimate the activation energies for the C–Br splitting, account has to be taken of the activation energy associated with the steps

$$CH_3{\cdot}CH{:}CH_2 + Br \longrightarrow CH_3{\cdot}CH{\cdot}CH_2Br$$
$$CH_3{\cdot}CH{:}CH_2 + Br \longrightarrow CH_3{\cdot}CHBr{\cdot}CH_2$$

Indirect evidence relating to these reactions comes from a study of the photo-addition of hydrogen bromide to olefins investigated by Vaughan, Rust, and Evans (*J. Org. Chem.*, 1942, **7**, 477). This reaction probably proceeds by the mechanism

$$HBr \xrightarrow{h\nu} H + Br$$
$$Br + CH_3{\cdot}CH{:}CH_2 \longrightarrow CH_3{\cdot}\dot{C}H{\cdot}CH_2Br$$
$$CH_3{\cdot}\dot{C}H{\cdot}CH_2Br + HBr \longrightarrow CH_3{\cdot}CH_2{\cdot}CH_2Br + Br$$

together with some chain-ending step. These authors found that in all cases the addition was exclusively abnormal in the Kharasch sense, which implies that the rate of bromine addition to the 1-position in propene vastly exceeds that to the 2-position. The equilibrium and kinetic behaviour are shown in Fig. 6, in which the reaction path is sketched in each case. It may be concluded from these arguments that $k_3^N \gg k_3^S$. This factor is possibly the most important in explaining the difference in behaviour between *n*- and *iso*-propyl bromide on pyrolysis, because if k_3^S is small, the chain mechanism will not be available to *iso*propyl bromide.

It is of interest to enquire as to the relevance to the bromides of the rules suggested by Barton *et al.* (*Trans. Faraday Soc.*, 1949, **45**, 725; *J.*, 1951, 2039) correlating mechanism and structure in the case of the chlorides. These authors have suggested that a chain mechanism will only obtain if neither the decomposing chloride nor the products of decomposition are inhibitors for the chain mechanism. Inhibition by the reactant is explained in terms of the nature of the radical produced by chlorine-atom attack upon the reactant. Thus whereas in 1 : 2-dichloroethane the radical $\dot{C}H{\cdot}Cl{\cdot}CH_2Cl$ is produced; in the case of the 1 : 1-dichloroethane the radical $CH_3{\cdot}\dot{C}Cl_2$ is formed. In the former case the product is a P radical, in the latter an S radical. Thus the 1 : 1-dichloroethane molecule is an inhibitor for its own chain decomposition. Neither of these rules appears to hold in the case of the bromides, for both 1 : 1- and 1 : 2-dibromoethane decompose normally by a chain mechanism (P. T. Good, unpublished work), and further, all primary bromides so far investigated have been shown to decompose partially by a chain mechanism, even though an olefinic inhibitor is one of the products of reaction. The explanation of the difference in behaviour is at least in part forthcoming, namely, in the first case the possibility of conversion of an S radical into a P radical, and in the second, the relative inefficiency of straight-chain olefins as inhibitors (P. J. Thomas, unpublished work). It is hoped in later communications to deal with the question of the chain mechanism in greater detail.

It remains to discuss the observed ratio of final to initial pressure (<2), the fall in rate constant as the reaction proceeds, and the enhanced fall in the presence of added propene. All these facts are consistent with the existence of an equilibrium $C_3H_7Br \rightleftharpoons C_3H_6 + HBr$. Reference to Fig. 1 shows that when, for example, 80% of the *iso*propyl bromide has reacted as determined by pressure measurements, 80% of the hydrogen bromide has been eliminated. This implies that the low value of the ratio of final to initial pressure cannot be due to any extensive polymerisation of the propene. Further, if the rate of reaction is given by

$$-\text{d}[C_3H_7Br]/\text{d}t = k_1[C_3H_7Br] - k_2[C_3H_6][HBr]$$

then, while the initial rates give a true measure of k_1, the log plots will be concave upwards and the departure from a straight line will be greater the higher the initial pressure and the higher the pressure of added propene.

The present technique was not considered suitable for investigating the equilibrium, because of dead-space errors. Thus, although the volume of the dead space was too small to account for the fact that only 80% of the bromide decomposes, it is considered that such an effect operates to an extent which would render any quantitative study of equilibrium of doubtful value.

Blades and Murphy (*J. Amer. Chem. Soc.*, 1952, **74**, 6219) have reported an investigation of the pyrolysis of *iso*propyl bromide using a flow system, with Szwarc's toluene-carrier gas technique (*J. Chem. Phys.*, 1949, **17**, 432). These authors covered a temperature range some 150° higher than that covered in the present work and arrived at a rate expression

$$k = 4{\cdot}0 \times 10^{13} \exp(-47{,}700/\boldsymbol{R}T)$$

in very good agreement with the values reported here. As might have been expected from the reported absence of a free-radical mechanism in this reaction (*ibid.*, 1951, **19**, 977), Blades and Murphy could detect no dibenzyl in their reaction products. This compound would have been produced by the steps

$$C_3H_7Br \longrightarrow C_3H_7 + Br \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$Br + CH_2Ph \longrightarrow CH_2Ph + HBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$
$$C_3H_7 \longrightarrow C_3H_6 + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$
$$H + CH_2Ph \longrightarrow CH_2Ph + H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$
$$2CH_2Ph \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}Ph \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Reaction (1), as explained on p. 983, would have an activation energy of about 676 kcal., the rate being reasonably expressed as $k = 10^{13} \exp(-67{,}600/\boldsymbol{R}T)$. This process would thus be completely insignificant compared with the unimolecular elimination of hydrogen bromide. It could thus be confidently predicted that any inert carrier gas would have been sufficient in the flow investigation.

One of us (P. J. T.) acknowledges the award of a D.S.I.R. Maintenance Grant during the tenure of which this work was completed. Also both authors would like to express their appreciation of the encouragement and advice afforded them by discussions with Professor C. K. Ingold, F.R.S.

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University College, London, W.C.1. [*Received, September 29th*, 1954.]

The Constitution of Conessine. Part VIII. Reaction of Cholesteryl Toluene-*p*-sulphonate with Liquid Ammonia.*

By R. D. Haworth, L. H. C. Lunts, and J. McKenna.

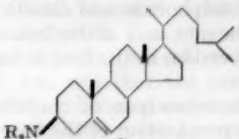
[Reprint Order No. 5914.]

The ammonolysis of cholesteryl toluene-*p*-sulphonate yields 3α-amino-cholest-5-ene and dicholesterylamines or isomers in addition to 3β-amino-cholest-5-ene and 6β-amino-3 : 5-*cyclo*cholestane which have already been described as products of the reaction.

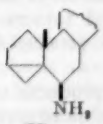
The reaction of cholesteryl toluene-*p*-sulphonate with liquid ammonia was first investigated by Julian, Magnani, Meyer, and Cole (*J. Amer. Chem. Soc.*, 1948, **70**, 1834) who obtained cholesterylamine, $C_{27}H_{47}N$ (I; R = H), and 6-amino-3 : 5-*cyclo*cholestane (II), the constitution of which was established by degradation to 3β-chlorocholestan-6-one. The same two products were obtained by Haworth, McKenna, and Powell (*J.*, 1953, 1110), together with a third base, m. p. 190°. Methylation of the mixture of amines left after separation of the 3 : 5-*cyclo*-base (II) yielded 3β-dimethylaminocholest-5-ene (I; R = Me)

* Part VII, *J.*, 1954, 967.

and an isomeric base, m. p. 70—71°; the same two methylated products were obtained from the reaction of cholesteryl toluene-*p*-sulphonate with dimethylamine. The constitution of the former, (I; R = Me), was firmly established by infra-red, ultra-violet, and optical rotation data, by Hofmann degradation to cholesta-3 : 5-diene (Haworth, McKenna, and Whitfield, *J.*, 1953, 1102; Favre, Haworth, McKenna, Powell and Whitfield, *ibid.*, p. 1115), and by hydrogenation to 3β-dimethylaminocholestane (III) (Dodgson and Haworth, *J.*, 1952, 167). This work was regarded as affording evidence for structure (I; R = H) for cholesterylamine, as the latter appeared to have yielded the dimethylamino-derivative (I; R = Me) on methylation, while the base of m. p. 190° was thought to correspond (after methylation) to the product of m. p. 70—71°. Further, on the basis



(I)



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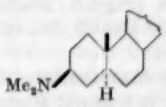
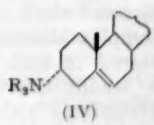


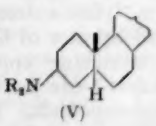
(III)

of Shoppee's generalisation (*J.*, 1946, 1147) it was thought unlikely that these new amines, and likewise a corresponding series encountered with a pregnane framework, carried an α-orientated basic group at $C_{(3)}$ (as in IV). The latter supposition appeared to be borne out by hydrogenation of the base, $C_{29}H_{51}N$, m. p. 70—71°; the product, $C_{29}H_{53}N$, m. p. 73—74°, was not identical with 3α- or 3β-dimethylaminocholestane, and from a further generalisation (quoted by, *inter alia*, Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 545) it was thought unlikely that hydrogenation of (IV; R = Me) would yield predominantly the coprostane derivative (V; R = Me). It appeared desirable, however, to re-examine the ammonolysis reaction and the bases of undetermined structure.

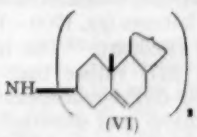
While this work was in progress, Šorm, Lábler, and Černý (*Chem. Listy*, 1953, **47**, 418) reported that the tertiary base, m. p. 73—74°, independently obtained by the method described above, was also formed on reaction of dimethylamine with coprostan-3β-yl toluene-*p*-sulphonate; the base, m. p. 73—74°, is thus 3α-dimethylaminocoprostane (V; R = Me), derived by hydrogenation of 3α-dimethylaminocholest-5-ene (IV; R = Me); a more detailed treatment of the stereochemistry of these and other steroidal amines has recently * (*Chem. Listy*, 1954, **48**, 1058) been given by the Czech authors. The Hofmann degradation of the base, m. p. 70—71°, to cholesta-3 : 5-diene previously described by Haworth, McKenna, and Powell (*loc. cit.*) is in accord with the formulation (IV; R = Me)



(IV)



(V)



(VI)

and we have found that the infra-red (maxima at 796, 827, and 1660 cm.$^{-1}$; cf. Haworth, McKenna, and Whitfield, *loc. cit.*; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402) and ultra-violet absorption ("end absorption" similar to that of 3β-dimethylaminocholest-5-ene; cf. Haworth, McKenna, and Whitfield, *loc. cit.*; Bladon, Henbest, and Wood, *J.*, 1952, 2737) and optical rotation ["Δ value" (Barton and Klyne, *Chem. and Ind.*, 1948, 755) of the unsaturated amine relative to 3α-dimethylaminocholestane is −223°, while the value for the epimeric 3β-dimethylaminocholest-5-ene relative to 3β-dimethylaminocholestane is −227°] support this structure. It thus appeared that in the reaction of cholesteryl toluene-*p*-sulphonate with ammonia (or dimethylamine) some inversion at $C_{(3)}$ occurred, and that hydrogenation of 3α-substituted Δ^5-steroids could

* In correspondence (June, 1953) Drs. Šorm and Lábler assigned structure (IV; R = Me) to the base, $C_{29}H_{51}N$, m. p. 70—71°, and kindly informed us that stereochemical considerations were not dealt with in their earlier paper as they were still working on this subject.

lead to A/B-*cis*-dihydro-derivatives predominantly. Examples of the formation of coprostanes by hydrogenation of 3α-substituted cholest-5-enes are given by Lewis and Shoppee (*Chem. and Ind.*, 1953, 897; 1954, 933).

Other examples of each phenomenon have recently been observed. Thus the reaction of cholesteryl toluene-*p*-sulphonate with diethyl sodiomalonate in boiling toluene yields some cholest-5-en-3α-yl-malonic ester in addition to the isomeric 3β- and 3 : 5-*cyclo*-compounds (Shoppee and Stephenson, *J.*, 1954, 2230; cf. Kaiser and Svarz, *J. Amer. Chem. Soc.*, 1949, **71**, 517, and earlier papers). The three reaction products of cholesteryl chloride with benzylamine were similarly formulated * by Vavasour, Bolker, and McKay (*Canad. J. Chem.*, 1952, **30**, 933); and we have recently established (unpublished work) that the reaction between pregn-5-en-3β-yl toluene-*p*-sulphonate and dimethylamine, and that between pregn-5 : 20-dien-3β-yl toluene-*p*-sulphonate and methylamine (Haworth, McKenna, and Powell, *loc. cit.*), also proceed with inversion, in the first instance virtually exclusively so.

In our re-examination of the products of the ammonolysis of cholesteryl toluene-*p*-sulphonate it was not found possible to repeat the preparation of the base, m. p. 190°; instead, a base $C_{54}H_{91}N$, m. p. 250° (decomp.), $[\alpha]_D$ −31°, of which the earlier product was probably an impure specimen, was obtained by chromatography or fractional crystallisation, together with an isomer, m. p. 172°, $[\alpha]_D$ −9°. These bases are probably isomeric dicholesterylamines (VI) (or perhaps one nucleus may have the 3 : 5-*cyclo*-structure); their formation is favoured by longer reaction times (up to 20 hours at 95°). Fractions, m. p. *ca.* 90°, also obtained by chromatography of the ammonolysis mixtures appeared to consist essentially of 3α- and/or 3β-aminocholest-5-ene. Direct isolation of pure samples of these epimeric bases proved difficult, but their *N*-acetyl derivatives were easily separated by fractional crystallisation. 3β-Acetamidocholest-5-ene readily yielded cholesterylamine (I; R = H) on hydrolysis with alcoholic potassium hydroxide; hydrolysis of the 3α-acetamido-epimer gave a basic oil which could not be crystallised but yielded 3α-dimethylaminocholest-5-ene (IV; R = Me) on methylation. Hydrogenation of 3α-acetamidocholest-5-ene did not yield predominantly the A/B-*cis*-dihydro-derivative as in the case of the related tertiary base; instead, 3α-acetamidocholestane was obtained, together with an approximately equal proportion of a second acetyl derivative, presumably 3α-acetamidocoprostane. 3α-Acetamidocholestane was prepared for comparison by acetylation of the ammonolysis product of cholestan-3β-yl toluene-*p*-sulphonate.

The epimeric 3-aminocholest-5-enes readily afforded *iso*propylidene derivatives on recrystallisation from acetone, which was somewhat unexpected. The infra-red absorption curve of neither derivative exhibited a band in the region characteristic of C=O stretching in non-conjugated ketones (*ca.* 1700—1750 cm.$^{-1}$) but a strong band which may be ascribed to C=N stretching (Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 227) rather than C=C stretching appeared in each case at 1660 cm.$^{-1}$. 3α- and 3β-*iso*Propylideneaminocholest-5-ene were readily converted into the appropriate acetamido- and dimethylamino-compounds. Hydrolysis with dilute hydrochloric acid gave the expected yield (*ca.* 70%, corresponding to trial runs) of acetone (as 2 : 4-dinitrophenylhydrazone) and the corresponding primary amine. Only by this procedure have we been able to obtain pure samples of 3α-aminocholest-5-ene (IV; R = H).

6β-Amino-3 : 5-*cyclo*cholestane (II) was isolated as before (Julian, Magnani, Meyer, and Cole, *loc. cit.*; Haworth, McKenna, and Powell, *loc. cit.*) from the ammonolysis mixtures; the melting point (85°) is higher than was previously recorded (77—79°). The ratio of 3 : 5-*cyclo*-amine to total bases formed by ammonolysis varied to some extent with the conditions: lower temperatures or shorter heating gave more *cyclo*-base. The stereochemical orientation at $C_{(6)}$ of this amine has not been determined by previous workers,

* Professor C. W. Shoppee has kindly sent us the MSS. of two papers; in one it is conclusively demonstrated that some inversion at $C_{(3)}$ takes place in this reaction, and additional evidence is presented on some allied substitutions at $C_{(3)}$ likewise accompanied by inversion. In the second paper is described the preparation of cholesterylamine by degradation of the corresponding carboxylic acid, a synthesis which furnishes additional evidence of stereochemical configuration of the amine (I; R = H).

but from analogy with similar rearrangement products (Shoppee and Summers, *J.*, 1952, 3361) it may be assigned the β-configuration as in (II). Methylation of the primary amine, $C_{27}H_{47}N$, with formaldehyde and formic acid yielded a basic oil, $[\alpha]_D$ +54°, from which a hydrochloride, $C_{29}H_{51}N,HCl,H_2O$, m. p. 166—167° (m. p. 206—207°, $[\alpha]_D$ +44°, when anhydrous) was prepared; this tertiary base is probably identical with an oily amine, $[\alpha]_D$ +61° (hydrochloride, m. p. 198°, $[\alpha]_D$ +45°) prepared by Šorm, Lábler, and Černý (*loc. cit.*) from cholesteryl toluene-*p*-sulphonate and dimethylamine and ascribed a **3 : 5**-*cyclo*-structure by them. Some cholesterol was also isolated from the methylation mixture. Treatment of the tertiary base in acetone with methyl iodide yielded cholesteryl iodide and tetramethylammonium iodide in addition to the expected quaternary salt; the last-named product, however, was unaffected when heated in acetone with or without addition of methyl iodide.

The alkaloid conessine has a **5 : 6**-double bond and it seems likely (Haworth, McKenna; and Whitfield, *loc. cit.*) that the acetic–sulphuric acid conversion into the isomer *neo*-conessine involves this unsaturated centre. Attempts were therefore made to isomerise 3β-dimethylaminocholest-5-ene by similar treatment, but complications were introduced by the low solubility of this base in the acid medium, and no definite product was isolated.

Experimental

Specific rotations were determined in $CHCl_3$.

Ammonolysis of Cholesteryl Toluene-p-*sulphonate.*—The ester was heated for 5—20 hr. at 90—95° with a large excess of liquid ammonia, and the basic reaction products were separated as previously described (Julian, Magnani, Meyer, and Cole, *loc. cit.*; Haworth, McKenna, and Powell, *loc. cit.*) into two fractions with hydrochlorides respectively soluble and insoluble in ether.

Base, m. p. 250°, *and Isomer, m. p.* 172°.—Mixed bases from hydrochlorides (5·3 g.) insoluble in ether, from an ammonolysis which had proceeded for 15 hr. at 95°, were chromatographed on alumina (Spence's Type H activated at 160° for 10 min.; 100 g.); on elution with light petroleum (b. p. 40—60°) a fraction (1 g.), m. p. 170—235°, was obtained, which on recrystallisation from the same solvent yielded a *base* as colourless needles (0·2 g.), m. p. 250° (decomp.), $[\alpha]_D$ −31° (*c*, 2·5) [Found: C, 86·0; H, 12·2; N, 2·1%; *M* (Rast), 753. $C_{54}H_{91}N$ requires C, 86·1; H, 12·1; N, 1·9%; *M*, 753]. Further elution with ether–chloroform gave a waxy solid (3·3 g.), m. p. 90—98° with previous softening; this fraction (epimeric 3-amines) resisted further attempts at direct purification. The mother-liquors from recrystallisation of the base, m. p. 250°, yielded an isomeric *base* as colourless needles (0·25 g.), m. p. (from methanol) 168—170°, raised to 172°, $[\alpha]_D$ −9° (*c*, 1·8), on further recrystallisation [Found: C, 85·8; H, 12·1; N, 1·9%; *M* (Rast), 765]. This amine was occasionally obtained from early chromatographic fractions and, like the isomer of m. p. 250°, was also isolated by fractional crystallisation of the total ether-insoluble hydrochlorides from methanol, in which the hydrochlorides of the higher-melting C_{54} amines were least soluble.

Treatment of the base, m. p. 250°, with boiling acetic anhydride gave an N-*acetyl* derivative, which separated from acetone in small colourless needles, m. p. 179° (Found: C, 83·6; H, 11·7. $C_{56}H_{93}ON$ requires C, 84·5; H, 11·7%). Methylation of the base (50 mg.) with formic acid (90%; 1 c.c.) and formaldehyde (40%; 1 c.c.) for 7·5 hr. at 100° yielded the N-*methyl* derivative as an oil (53 mg.) which on crystallisation from ether–acetone formed colourless prismatic needles, m. p. 159°, $[\alpha]_D$ −37° (*c*, 2·4) (Found: C, 85·7; H, 12·3; N, 1·8. $C_{55}H_{93}N$ requires C, 86·0; H, 12·1; N, 1·8%). Treatment of the base, m. p. 250° (43 mg.), in ether (20 c.c.) with N-hydrochloric acid (10 c.c.) and sodium nitrite (0·5 g.) for 7 hr. at 0° gave a product (8 mg.), colourless needles (from ether), m. p. 260° (depressed to 232—236° on admixture with the original amine), which gave a positive Liebermann nitroso-reaction.

The amine, m. p. 172°, described above yielded an N-*methyl* derivative, colourless plates (from ether–methanol), m. p. 186°, depressed to 169° on admixture with the base of m. p. 172° (Found: N, 1·7. $C_{55}H_{93}N$ requires N, 1·8%).

N-iso*Propylidene Derivatives of Epimeric* 3-*Aminocholest*-5-*enes from Ammonolysis Mixture.*—Bases (2 g.) with ether-insoluble hydrochlorides, from an ammonolysis which had proceeded for 5 hr. at 90°, on fractional crystallisation from acetone yielded successively crude C_{54} amine (50 mg.), m. p. 248—250° (decomp.), 3β-iso*propylideneaminocholest*-5-*ene* in colourless needles (0·35 g.), m. p. 136—138° raised to m. p. 140° on further recrystallisation, $[\alpha]_D$ −33° (*c*, 3·6) (Found: C, 84·4; H, 11·7; N, 3·7. $C_{30}H_{51}N$ requires C, 84·7; H, 12·0; N, 3·3%), and

3α-*iso*propylideneaminocholest-5-ene in colourless prisms (0·8 g.), m. p. 80—94° raised to m. p. 96° on further recrystallisation, $[\alpha]_D$ +7° (*c*, 3·7) (Found: C, 84·3; H, 11·7; N, 3·3%).

3β-*iso*Propylideneaminocholest-5-ene and the derived 3β-aminocholest-5-ene described below, but not the 3α-epimers, readily yielded precipitates with digitonin in alcohol. Acetylation and methylation of the 3β-*iso*propylidene derivative gave respectively 3β-acetamidocholest-5-ene, colourless plates (from methanol), m. p. 238°, undepressed on admixture with a sample obtained as described below, and 3β-dimethylaminocholest-5-ene, colourless needles (from acetone), m. p. and mixed m. p. 148°. Similar treatment of 3α-*iso*propylideneaminocholest-5-ene yielded 3α-acetamido-, colourless needles (from acetone), m. p. 180°, and 3α-dimethylamino-cholest-5-ene, colourless plates (from acetone), m. p. 68°, both undepressed on admixture with authentic specimens.

Epimeric 3-*Acetamidocholest-5-enes from Ammonolysis Mixture.*—Bases (2 g.) with ether-insoluble hydrochlorides from an ammonolysis (which had run for 7 hr. at 90°) in ether (5 c.c.) were treated with acetone (50 c.c.), the insoluble crude C_{54} amines were separated, and the residue was treated with boiling acetic anhydride for 10 min. Fractional crystallisation of the product (1·0 g.) from methanol gave 3β-acetamidocholest-5-ene as colourless plates (0·15 g.), m. p. 236—238° raised to m. p. 240—241° on further recrystallisation (Windaus and Adamla, *loc. cit.*, give m. p. 243—244°; Julian, Magnani, Meyer, and Cole, *loc. cit.*, give m. p. 238—242°), $[\alpha]_D$ −43° (*c*, 3·5). The mother-liquors yielded 3α-acetamidocholest-5-ene as colourless needles, (0·6 g.), m. p. 160—170° raised to m. p. 184° on recrystallisation from acetone, $[\alpha]_D$ −53° (*c*, 4·7) (Found: C, 81·1; H, 11·7; N, 3·3. Calc. for $C_{29}H_{49}ON$: C, 81·5; H, 11·5; N, 3·3%). Vavasour, Bolker, and McKay (*loc. cit.*) give m. p. 188—189°.

3β-*Aminocholest-5-ene.*—(*a*) 3β-*iso*Propylideneaminocholest-5-ene (59 mg.) was treated under reflux with 2N-hydrochloric acid (20 c.c.) for 1 hr.; steam-distillation then yielded acetone [2 : 4-dinitrophenylhydrazone (22 mg., 68%), m. p. and mixed m. p. 120—122°]. In a trial run at similar concentrations, 71% of acetone was recovered as 2 : 4-dinitrophenylhydrazone. The basic product (37 mg.) from the hydrolysis mixture was recrystallised from methanol and distilled at 140° (bath)/0·01 mm., and the 3β-aminocholest-5-ene obtained as colourless needles, m. p. 96°, $[\alpha]_D$ −34° (*c*, 2·7) (Found: N, 3·5. Calc. for $C_{27}H_{47}N$: N, 3·6%). The m. p. rose to 100—160° after the base had been kept for some time in a stoppered tube. Windaus and Adamla (*loc. cit.*) record m. p. 98° for this base, and Julian, Magnani, Meyer, and Cole (*loc. cit.*) give m. p. 89—94°, $[\alpha]_D$ −26°. Acetylation and methylation gave the acetyl and dimethyl derivative, m. p. 234—235° and 147—148° respectively.

(*b*) 3β-Acetamidocholest-5-ene (100 mg.) was treated with ethanolic potassium hydroxide (20%; 10 c.c.) for 27 hr. at 140°, and the basic reaction product crystallised from methanol. The colourless needles of 3β-aminocholest-5-ene had m. p. 92—94°.

3α-*Aminocholest-5-ene.*—3α-*iso*Propylideneaminocholest-5-ene (44 mg.) was hydrolysed by the method described above, yielding acetone (74% as 2 : 4-dinitrophenylhydrazone) and 3α-*aminocholest-5-ene* (32 mg.), colourless needles [on sublimation at 160° (bath)/0·01 mm.], m. p. 100—101°, $[\alpha]_D$ −44° (*c*, 2·8) (Found: N, 3·6. $C_{27}H_{47}N$ requires N, 3·6%), which was conveniently purified through the *hydrochloride*, colourless plates from methanol–ether, m. p. 288—290° (Found: Cl, 8·2. $C_{27}H_{47}N,HCl$ requires Cl, 8·4%). Vavasour, Bolker, and McKay (*loc. cit.*) give m. p. 220—230° for this salt. On admixture of the amine, m. p. 100—101°, with the *iso*propylidene derivative, m. p. 96°, the mixed m. p. was 80—92°. After being kept for some time in a stoppered tube, the base had m. p. 96—110°. Acetylation and methylation of the base gave the acetyl and dimethyl derivatives, m. p. 180—182° and 67—69° respectively.

Hydrogenation of 3α-*Acetamidocholest-5-ene.*—The acetyl compound (87 mg.) in acetic acid (5 c.c.) was hydrogenated in presence of 15% palladised charcoal (60 mg.) (uptake at 27°/730 mm., 7·1 c.c. Calc. for one double bond, 5·2 c.c.). Fractional crystallisation of the product from ether gave colourless needles (30 mg.) of 3α-acetamidocholestane, m. p. 213—214° undepressed on admixture with an authentic specimen prepared as described below, and colourless needles (40 mg.) of an *isomer*, m. p. 180—181° (Found: C, 81·0; H, 11·8; N, 3·3. $C_{29}H_{51}ON$ requires C, 81·1; H, 11·9; N, 3·3%) depressed to 160—174° on admixture with 3α-acetamidocholest-5-ene, m. p. 184°.

3α-*Acetamidocholestane.*—Cholestan-3β-yl toluene-*p*-sulphonate (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147) (500 mg.) was heated with excess of liquid ammonia for 10 hr. at 90°; the basic reaction product on acetylation gave 3α-acetamidocholestane (140 mg.) which separated from acetone in colourless needles, m. p. 215—216°, $[\alpha]_D$ +33° (*c*, 1·3) (Found: C, 80·9; H, 11·8; N, 2·9%).

Methylation of 6β-*Amino*-3 : 5-cyclo*cholestane.*—Ether-soluble hydrochlorides from the

ammonolysis of cholesteryl toluene-*p*-sulphonate yielded on basification the primary 3 : 5-*cyclo*amine, colourless needles (from pentane), m. p. 84—85°, $[\alpha]_D$ +36° (*c*, 5·5) (Found : C, 84·1; H, 12·3; N, 3·2. Calc. for $C_{27}H_{47}N$: C, 84·2; H, 12·2; N, 3·6%). Julian, Magnani, Meyer, and Cole (*loc. cit.*) give m. p. 77—79°, $[\alpha]_D$ +34°. Methylation of the primary amine (1 g.) with formaldehyde and formic acid in the usual way yielded an oil (1·1 g.), $[\alpha]_D$ +37°, which was chromatographed in light petroleum (b. p. 40—60°; 25 c.c.) on alumina (Spence's Type H neutralised with ethyl acetate, washed with water, and reactivated at 240°; 16·5 g.). A basic oil (0·8 g.), $[\alpha]_D$ +48°, was obtained, followed by colourless needles (0·09 g.), m. p. 120—132°, raised to 146—147° on recrystallisation from methanol and undepressed on admixture with cholesterol; for further characterisation the acetate was prepared; it had m. p. 112—113°, undepressed on admixture with cholesteryl acetate. The basic oil was purified by further chromatography until the $[\alpha]_D$ value was +51°, and then converted into the hydrated *hydrochloride*, colourless rods (from acetone), m. p. 166—167° (rapid heating) (Found : C, 74·5; H, 11·8. $C_{29}H_{51}N,HCl,H_2O$ requires C, 74·4; H, 11·6%), m. p. 206—207° (slow heating, or after drying at 60—80°/0·05 mm. over P_2O_5), $[\alpha]_D$ +44° (*c*, 2·6) [Found (in anhydrous salt) : C, 77·6 H, 11·7 N, 2·8; Cl, 7·5. Calc. for $C_{29}H_{51}N,HCl$: C, 77·4; H, 11·6; N, 3·1; Cl, 7·9%]. The 6β-dimethylamino-3 : 5-*cyclo*cholestane on recovery from the hydrochloride had b. p. 164—166°/0·05 mm., $[\alpha]_D$ +54° (*c*, 1·3). This base (75 mg.) in dry acetone (10 c.c.) was refluxed with dry methyl iodide (5 c.c.) for 3·5 hr., the solvents were evaporated, and the residue was extracted with ether (25 c.c.); the extract yielded cholesteryl iodide (20 mg.), colourless rods (from acetone), m. p. 104·5—105° (Found : C, 65·3; H, 9·0; I, 25·3. Calc. for $C_{27}H_{45}I$: C, 65·3; H, 9·1; I, 25·6%) undepressed on admixture with a specimen prepared by the method of Burckhardt, Helferich, and Günther (*Ber.*, 1939, **72**, 338). The residue from the methylation, after extraction with ether, was separated by trituration with acetone (10 c.c.) into a residue of tetramethylammonium iodide (15 mg.) which sublimed with some decomposition at 340°/760 mm. (Found : I, 63·2. Calc. for $C_4H_{12}NI$: I, 63·2%) and was converted into the picrate, m. p. 321° (Found : N, 18·3. Calc. for $C_{10}H_{14}O_7N_4$: N, 18·6%) (Kohn and Grauer, *Monatsh.*, 1913, **34**, 1751, give m. p. 318—320°), and 6β-*dimethylamino*-3 : 5-cyclo*cholestane methiodide*, colourless needles (from acetone), m. p. 206—207° (Found : C, 64·5; H, 9·7; N, 2·5; I, 22·3. $C_{30}H_{54}NI$ requires C, 64·9; H, 9·7; N, 2·5; I, 22·9%).

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 25th*, 1954.]

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*Cyclic Amidines. Part IV.** 5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-*endo*-*methylenephenhomazine and Tröger's Base.*

By F. C. COOPER and M. W. PARTRIDGE.

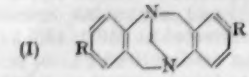
[Reprint Order No. 5938.]

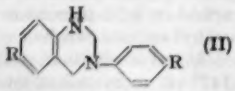
5 : 11-Dichlorophenhomazine and its 2 : 8-dimethyl homologue are reduced with lithium aluminium hydride to the corresponding 5 : 6 : 11 : 12-tetrahydrophenhomazines, which with formaldehyde afford 5 : 6 : 11 : 12-tetrahydro-5 : 11-*endo*methylene- and 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethyl-5 : 11-*endo*methylene-phenhomazine (Tröger's base) respectively.

THE ring system 5 : 11-*endo*methylene-5 : 6 : 11 : 12-tetrahydrophenhomazine {5 : 11-6*H* : 12*H*)-methanodibenzo[*b*, *f*][1 : 5]diazocine; Ring Index no. 2651} (I; R = H) has hitherto been known in the form of its 2 : 8-dimethyl derivative, Tröger's base (I; R = Me) (Tröger, *J. pr. Chem.*, 1887, **36**, 227; Spielman, *J. Amer. Chem. Soc.*, 1935, **57**, 583), and a few other derivatives (Miller and Wagner, *ibid.*, 1941, **63**, 832; Smith and Schubert, *ibid.*, 1948, **70**, 2656). In confirmation of the structure proposed, Spielman (*loc. cit.*) prepared the base by treatment of 1 : 2 : 3 : 4-tetrahydro-6-methyl-3-*p*-tolylquinazoline (II; R = Me) with formaldehyde. The success of this preparation appears to depend on the

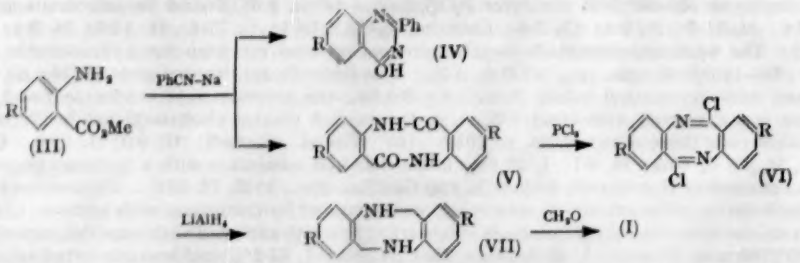
* Part III, *J.*, 1955, 510.

reactivity of the 2′-position, since the quinazolines (II; R = OMe or OEt) afford the corresponding analogues of Tröger's base (I; R = OMe or OEt), whereas the eight-membered ring is not formed from the halogenated quinazolines (II; R = Cl or Br) (Miller and Wagner, *loc. cit.*). Wagner (*J. Amer. Chem. Soc.*, 1935, **57**, 1296) speculated on the


(I)

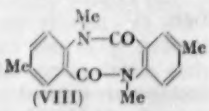

(II)

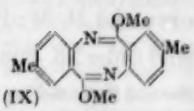
possibility of a more direct synthesis by the condensation of formaldehyde and 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethylphenhomazine (VII; R = Me), but this compound was not then available. We have now investigated the synthesis of 5 : 6 : 11 : 12-tetrahydrophenhomazines and their conversion into their 5 : 11-*endo*methylene derivatives.

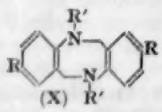


Methyl 5-methylanthranilate (III; R = Me) reacts exothermally with benzonitrile in the presence of " powdered " sodium to furnish (cf. Part I, *J.*, 1954, 3429), in addition to 4-hydroxy-6-methyl-2-phenylquinazoline (IV; R = Me), 2 : 8-dimethyldianthranilide (V; R = Me) which affords its *NN*′-dimethyl derivative (VIII) with methyl sulphate. 6 : 12-Dichloro-2 : 8-dimethylphenhomazine (VI; R = Me) results when the foregoing dianthranilide is brought into reaction with phosphorus pentachloride; experiments with dianthranilide itself (V; R = H) indicated that an analogous reaction cannot be effected with thionyl chloride or phosphorus oxychloride. Interaction of the dichloro-compound (VI; R = Me) and sodium methoxide gives the dimethoxyphenhomazine (IX).

Schroeter (*Ber.*, 1919, **52**, 2224) has reported his inability to reduce 6 : 12-dichlorophenhomazine (VI; R = H). We find that most of the compound is recovered unchanged after treatment of it with Raney alloy and alkali. Attempts to reduce dianthranilide with hydriodic acid without fission of the ring system were also unsuccessful. However,


(VIII)


(IX)


(X)

dichlorophenhomazines (VI; R = H or Me) furnish 5 : 6 : 11 : 12-tetrahydrophenhomazines (VII; R = H or Me) when lithium aluminium hydride is employed as reducing agent. These tetrahydrophenhomazines react readily with formaldehyde to yield their 5 : 11-*endo*methylene derivatives (I; R = H or Me). The 2 : 8-dimethyl derivative (I; R = Me) is identical with Tröger's base.

In agreement with Spielman's observations (*loc. cit.*), we find that, on acylation or treatment with nitrous acid, 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethyl-5 : 11-*endo*methylenephenhomazine loses the *endo*methylene group to afford derivatives of tetrahydrophenhomazine (X; R = Me, R′ = Ac, Bz, or NO) identical with authentic specimens prepared directly from the tetrahydrophenhomazine (X; R = Me, R′ = H). The 5 : 11-dibenzoyl (X; R = H, R′ = Bz) and the 5 : 11-dinitroso-derivative (X; R = H, R′ = NO) may be obtained in a similar manner both directly from the secondary amine (X; R = R′ = H) and, with loss of the *endo*methylene group, from the tertiary amine (I; R = H). The

dinitrosamine (X; R = H, R′ = NO) could not be induced to undergo the Fischer–Hepp rearrangement.

Experimental

Spectroscopic measurements were made in absolute ethanol.

5 : 6 : 11 : 12-*Tetrahydrophenhomazine*.—There was a mildly exothermic reaction when lithium aluminium hydride (0·5 g.) in ether (80 ml.) was added to a suspension of 6 : 12-dichlorophenhomazine (Schroeter, *loc. cit.*) (2·5 g.) in ether (50 ml.). After 4 hours' refluxing, excess of reductant was decomposed by ethyl acetate (5 ml.), water (50 ml.) was added, and the mixture was made alkaline with sodium hydroxide (7 g.). The ether-soluble fraction (2·05 g.) afforded 5 : 6 : 11 : 12-*tetrahydrophenhomazine* (1·45 g., 76%) as colourless needles, m. p. 138·5—139·5°, after two recrystallisation from light petroleum (b. p. 100—120°) (charcoal) [Found: C, 80·2; H, 6·8; N, 13·4%; *M* (Rast), 215. $C_{14}H_{14}N_2$ requires C, 79·95; H, 6·7; N, 13·3%; *M*, 210]. Light absorption: $\lambda_{max.}$ 206, 242, 290 mμ (ε 40,000, 13,400, 2900). The *dihydrochloride*, obtained as small prisms by the addition of concentrated hydrochloric acid to a solution of the base in ethanol, was very sparingly soluble and could not be recrystallised; it darkened above 260° and did not melt below 400° (Found: C, 59·1; H, 5·55; N, 9·6. $C_{14}H_{16}N_2Cl_2$ requires C, 59·35; H, 5·7; N, 9·9%). Interaction of the base in ethanol with picric acid gave the *dipicrate* as clusters of minute needles, m. p. 161—163° (Found: C, 47·0; H, 2·8; N, 16·6. $C_{26}H_{20}O_{14}N_8$ requires C, 46·7; H, 3·0; N, 16·75%).

The *diacetyl* derivative, prepared by boiling the base with acetic anhydride, crystallised from aqueous acetic acid as small prisms, m. p. 335—337° (Found: C, 73·5; H, 5·95; N, 9·75. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15; N, 9·5%).

Benzoylation under Schotten–Baumann conditions afforded 5 : 11-*dibenzoyl*-5 : 6 : 11 : 12-*tetrahydrophenhomazine* which crystallised from *n*-butanol as platelets, m. p. 306·5—307·5° (Found: C, 80·3; H, 5·55; N, 6·85. $C_{28}H_{22}O_2N_2$ requires C, 80·35; H, 5·3; N, 6·7%).

5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-*dinitrosophenhomazine* separated immediately on the addition of sodium nitrite to a solution of the base in dilute hydrochloric acid, and it crystallised from benzene as small prisms, m. p. 233—234° (Found: C, 62·9; H, 4·6; N, 20·2. $C_{14}H_{12}O_2N_4$ requires C, 62·65; H, 4·5; N, 20·9%). This compound gave a positive Liebermann nitroso-reaction.

5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-endo*methylenephenhomazine*.—To a cold mixture of concentrated hydrochloric acid (5 ml.), 40% formaldehyde solution (2 ml.), and ethanol (10 ml.) was added finely powdered 5 : 6 : 11 : 12-tetrahydrophenhomazine (0·5 g.). The solid (0·45 g.) which was slowly deposited was collected next day, dissolved in hot water, and treated with excess of ammonia; the precipitate (0·35 g.; m. p. 138—139°) on crystallisation from light petroleum (b. p. 100—120°) furnished the 5 : 11-endo*methylene* derivative as prisms, m. p. 138—139°; a mixed m. p. with 5 : 6 : 11 : 12-tetrahydrophenhomazine was 108—115°. A further quantity (0·1 g., m. p. 138—139°) was recovered from the filtrate from the reaction mixture (total yield 85%) [Found: C, 80·95; H, 6·4; N, 12·3%; *M* (Rast), 274. $C_{15}H_{14}N_2$ requires C, 81·0; H, 6·35; N, 12·6%; *M*, 222]. Light absorption: $\lambda_{max.}$ 203, 240, 280 mμ (ε 33,700, 6300, 1600). Its *hydrochloride* crystallised from dilute hydrochloric acid as small prisms which shrank at about 250° and darkened without melting up to 360°; when inserted into the heating bath at 300°, the compound effervesced and resolidified (Found: C, 69·2; H, 5·65. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·85%). The *picrate* was obtained as small prisms, m. p. 190—191° (decomp.), from *n*-butanol (Found: C, 56·1; H, 3·6. $C_{21}H_{17}O_7N_5$ requires C, 55·85; H, 3·8%).

The product of treatment of the foregoing base with nitrous acid had, after crystallisation from benzene, m. p. 233—234° alone or in admixture with 5 : 6 : 11 : 12-tetrahydro-5 : 11-dinitrosophenhomazine. The compound obtained on benzoylation as described for 5 : 11-dibenzoyl-5 : 6 : 11 : 12-tetrahydrophenhomazine was identical with this compound as shown by m. p. and mixed m. p.

2 : 8-*Dimethyldianthranilide*.—There was an exothermic reaction when methyl 5-methylanthranilate (38·8 g.), prepared by the Fischer–Speier esterification of 5-methylanthranilic acid, and benzonitrile (48·4 g.) were added to "powdered" sodium (10·8 g.) in dry benzene (125 ml.). When the spontaneous boiling had subsided, the mixture was refluxed for 5 hr. Ethanol (10 ml.) and water (150 ml.) were added. The insoluble material was collected, washed with dilute hydrochloric acid and with water, and fractionally crystallised from ethanol. 2 : 8-*Dimethyldianthranilide* (11·6 g., 37%) occurred as small rods, m. p. 298—299° (Found: C, 72·4; H, 5·5; N, 10·8. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). Light absorption: $\lambda_{max.}$ 210 mμ (ε 35,600). This compound was but sparingly soluble in aqueous sodium hydroxide.

The second product, **4-*hydroxy*-6-*methyl*-2-*phenylquinazoline*** (5·7 g.), separated as pale yellow needles, m. p. 265—266° (Found: C, 76·5; H, 4·9; N, 12·1. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1; N, 11·85%). Light absorption: $\lambda_{max.}$ 209, 237, 294 mμ (ε 28,700, 27,700, 16,000). Light absorption of 4-hydroxy-2-phenylquinazoline: $\lambda_{max.}$ 206, 237, 291 mμ (ε 25,100, 26,500, 14,300). A further quantity (3·1 g.) of the quinazoline was recovered by faintly acidifying the aqueous layer obtained in working up.

2 : 8 : N : N′-*Tetramethyldianthranilide*, prepared by treatment of the foregoing dianthranilide (0·4 g.) with methyl sulphate (0·5 ml.) and 2N-sodium hydroxide (10 ml.), crystallised from benzene–light petroleum (b. p. 80—100°) as needles, m. p. 254—255° (Found: C, 73·7; H, 6·1. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15%). Light absorption: $\lambda_{max.}$ 213 mμ (ε 31,100)

6 : 12-*Dichloro*-2 : 8-*dimethylphenhomazine*.—Finely powdered **2 : 8**-dimethyldianthranilide (7·45 g.) and phosphorus pentachloride (12·5 g.) were boiled together in chloroform (50 ml.) for 4 hr. After filtration, the solid (4·85 g.) which separated on concentration of the filtrate was crystallised from light petroleum (b. p. 100—120°) and afforded **6 : 12-*dichloro*-2 : 8-*dimethylphenhomazine*** (4·05 g., 48%) as prisms, m. p. 209—210° (Found: C, 63·7; H, 3·65; N, 9·3. $C_{16}H_{12}N_2Cl_2$ requires C, 63·35; H, 4·0; N, 9·25%).

6 : 12-*Dimethoxy*-2 : 8-*dimethylphenhomazine* was formed in 90% yield by boiling the foregoing dichloro-compound in methanolic sodium methoxide for 23 hr., and it crystallised from light petroleum (b. p. 100—120°) as prisms, m. p. 155—156° (Found: C, 73·4; H, 5·9; N, 9·4. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15; N, 9·5%). Light absorption: $\lambda_{max.}$ 204, 258 mμ (ε 47,100, 6600). Light absorption of **6 : 12**-dimethoxyphenhomazine: $\lambda_{max.}$ 203, 253 mμ (ε 46,100, 5900) and of **6 : 12**-diethoxyphenhomazine: $\lambda_{max.}$ 203, 252 mμ (ε 45,500, 6100); the values for these two compounds recorded in Part I (*loc. cit.*) are incorrect.

5 : 6 : 11 : 12-*Tetrahydro*-2 : 8-*dimethylphenhomazine*.—After **6 : 12**-dichloro-**2 : 8**-dimethylphenhomazine (2·7 g.) and lithium aluminium hydride (0·5 g.) had been brought into reaction for 2½ hr. as described for **5 : 6 : 11 : 12**-tetrahydrophenhomazine, the ether-soluble material (1·85 g.) was separated by treatment with aqueous lactic acid into a neutral fraction (0·6 g.), which was unchanged starting material, and a basic fraction (0·8 g., m. p. 197—201°). The latter on crystallisation from light petroleum (b. p 100—120°) afforded **5 : 6 : 11 : 12-*tetrahydro*-2 : 8-*dimethylphenhomazine*** as colourless leaflets, m. p. 205—206°, depressed to below 190° by the original dichloro-compound (Found: C, 80·6; H, 7·65; N, 11·7. $C_{16}H_{18}N_2$ requires C, 80·6; H, 7·6; N, 11·75%). Light absorption: $\lambda_{max.}$ 207, 242, 295 mμ (ε 46,900, 16,200, 3200). Prolongation of the period of reduction to 8½ hr. gave the desired product in 74% yield. Its ***dipicrate*** separated as small prisms, m. p. 162—164°, when the base and picric acid reacted in ethanol (Found: C, 48·1; H, 3·4. $C_{28}H_{24}O_{14}N_8$ requires C, 48·3; H, 3·45%).

Acetylation of the base with boiling acetic anhydride afforded **5 : 11**-diacetyl-**5 : 6 : 11 : 12**-tetrahydro-**2 : 8**-dimethylphenhomazine which separated as small prisms, m. p. 297—298°, from aqueous acetic acid (Found: N, 8·85. Calc. for $C_{20}H_{22}O_2N_2$: N, 8·7%). This compound did not depress the m. p. of the product of acetylation of Tröger's base, m. p. 297—298°, obtained by the method of Spielman who records (*loc. cit.*) m. p. 286—288°.

The dibenzoyl derivative, prepared under Schotten–Baumann conditions, occurred as platelets, m. p. 301—302°, from xylene (Found: C, 80·6; H, 5·9. Calc. for $C_{30}H_{26}O_2N_2$: C, 80·7; H, 5·85%). By this method, the same compound, m. p. and mixed m. p. 301—302°, was obtained from Tröger's base in 56% yield; by Spielman's method the yield was only 10%. Spielman records m. p. 290—291° for this compound.

On being treated with nitrous acid, this base afforded the **5**-dinitroso-derivative, m. p. 247—248°, undepressed on admixture with the compound obtained by Spielman's method from Tröger's base (Found: C, 65·0; H, 5·7. Calc. for $C_{16}H_{14}O_2N_4$: C, 64·85; H, 5·45%). Spielman records m. p. 246—247° (254—255° corr.) for this compound.

5 : 6 : 11 : 12-*Tetrahydro*-2 : 8-*dimethyl*-5 : 11-endo*methylenephenhomazine*, prepared from the corresponding tetrahydrophenhomazine and formaldehyde in 95% yield, was obtained as colourless needles, m. p. 136—137°, undepressed on admixture with Tröger's base prepared in 30% yield by Goecke's method (*Z. Elektrochem.*, 1903, **9**, 470). Light absorption: $\lambda_{max.}$ 205, 235, 285 mμ (ε 35,700, 8300, 2000); in hexane, $\lambda_{max.}$ 246, 290 mμ (ε 8200, 2200). Wepster (*Rec. Trav. chim.*, 1953, **72**, 661) records for Tröger's base in *iso*octane: $\lambda_{max.}$ 247·5, 291 mμ (ε 8490, 2230).

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Amides of Vegetable Origin. Part III. Structure and Stereochemistry of* neo*Herculin.*

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*neo*Herculin, a pungent insecticidal principle from *Zanthoxylum clava-herculis* L., is obtained as a pure, but extremely unstable, compound and shown to have the molecular formula $C_{16}H_{25}ON$. It contains four double bonds, three of them in a conjugated triene system. Complete hydrogenation gives *N-iso*butyldodecanamide. The fourth double bond is shown by spectroscopical evidence to be in the 2-position, and the position of the triene system in the chain located by oxidative degradation. *neo*Herculin is *N-iso*butyldodeca-2 : 6 : 8 : 10-tetraenamide. Its stereochemistry is discussed.

Another pungent and insecticidal fraction has been isolated and preliminary results suggest that this too contains *N-iso*butylpolyeneamides.

In Part I * it was shown that the bark of *Zanthoxylum clava-herculis* L. (family Rutaceae) † (southern prickly ash) contains an unstable secondary amide. This compound, named *neo*herculin, is highly insecticidal and has ultra-violet light absorption characteristic of a conjugated triene. The amide has now been obtained pure and its structure determined. A preliminary note concerning its structure has been published (Crombie, *Nature*, 1954, **174**, 833).

Southern prickly ash bark was extracted with light petroleum (b. p. 40—60°) and the active material concentrated by partition with nitromethane. Purification of the nitromethane extract led to gradual elimination of two important components of the bark, asarinin (I) and *N*-2-*p*-methoxyphenylethyl-*N*-methylcinnamamide (II), subsequently

(I; R = 3 : 4 : 1-CH_2O_2:C_6H_3·)

p-MeO·C_6H_4·CH_2·CH_2·NMe·CO·CH:CHPh
(II)

referred to as herclavin (for references see Part I). These are readily separable by crystallisations from ethanol and were obtained in 0·26% and 0·38% yield respectively. No other compounds could be detected. After all the asarinin and herclavin had been removed, the mother-liquors, on cooling to −50°, yielded *neo*herculin (0·025% yield).

*neo*Herculin is crystalline (m. p. 70°) but unstable in air. It is highly insecticidal to *Musca domestica* L. and *Tenebrio molitor* L. (adults) and is a strong sialogogue with a

MeCH=CH·CH=CH·CH=CH·$[CH_2]_3$·CH=CH·CO·NHBu^i, ...	λ 227 mμ	$\lambda_{max.}$	259	269	280 mμ
*neo*Herculin	ε 13,000	ε	31,500	43,500	36,000
(α)-Me·$[CH_2]_3$·CH=CH·CH=CH·CH=CH·$[CH_2]_7$·CO_2H [1]	λ 226 mμ	$\lambda_{max.}$	261	271	281 mμ
	ε 4,000	ε	36,000	47,000	38,000
(β)-Me·$[CH_2]_3$·CH=CH·CH=CH·CH=CH·$[CH_2]_7$·CO_2H [1]	λ 226 mμ	$\lambda_{max.}$	259	268	279 mμ
	ε 5,500	ε	47,000	61,000	49,000
Me·$[CH_2]_6$·CH=CH·CO·NHBu^i [2]	$\lambda_{max.}$ 226 mμ				
	ε 10,300				
Me·$[CH_2]_6$·CH=CH·CO·NHBu^i [2]	$\lambda_{max.}$ 226 mμ				
	ε 10,000				

c = *cis*; t = *trans*. [1] Crombie and Taylor, *J.*, 1954, 2816. [2] Crombie, Part I.

characteristic burning taste. It has an empirical formula $C_{16}H_{25}ON$ and microhydrogenation reveals four double bonds. The infra-red spectrum (paraffin mull) shows it to be a monosubstituted amide [NH(stretching), 3260 cm.$^{-1}$, 3070 cm.$^{-1}$; amide A (carbonyl), 1626 cm.$^{-1}$; amide B, 1559 cm.$^{-1}$]. On hydrolysis with ethanolic hydrochloric acid, *iso*butylamine was obtained, but because of its instability the polyunsaturated acid was

* Parts I and II, *J.*, 1952, 2997, 4338.

† The spelling *Xanthoxylum*, which is frequently encountered in the literature, was used in Part I. The name originally given to the genus was *Zanthoxylum*, and by convention this spelling is correct. Dr. D. A. H. Taylor kindly provided this information.

not isolated. Direct comparison of octahydro*neo*herculin with synthetic *N-iso*butyldodecanamide showed them to be identical, thus establishing an unbranched chain for the acid fragment.

Since a saturated amine is produced by hydrolysis of *neo*herculin, all four double bonds lie in the chain of the acid. Ultra-violet light absorption (Table) shows that three of these are conjugated and that this unit is not further conjugated with the amide function. Nevertheless, the intensity of the C=C stretching vibration in the infra-red demonstrates that the amide grouping has αβ-unsaturation. (Experiments on the elaeostearic acids confirm that an internal triene system gives only weak absorption.) The position of the C=O stretching frequency (1626 cm.$^{-1}$) is also in agreement. It was shown in Parts I and II that αβ-unsaturation lowers the stretching frequency from 1642—1644 cm.$^{-1}$ to 1626—1634 cm.$^{-1}$ in a series of closely related *iso*butylamides. In confirmation, the ultra-violet absorption data (see Table) show that, when compared with an αβ-saturated conjugated triene (β-elaeostearic acid), *neo*herculin has a much higher ε value at 227 mμ (difference ~9000); this agrees reasonably with the ε at 227 mμ of simpler αβ-unsaturated *iso*butylamides.

The results leave structures (III—V) as possible for *neo*herculin, and of them *N-iso*butyldodeca-2 : 6 : 8 : 10-tetraenamide (III) is correct because ozonolysis yields acetaldehyde. *neo*Herculin is thus closely related to another insecticidal sialogogue, affinin (VI), which was isolated from *Heliopsis longipes* (A. Gray) Blake by Acree, Jacobson, and Haller (*J. Org. Chem.*, **1945**, **10**, 235, 449; **1947**, **12**, 731).

Me·[CH=CH]$_3$·CH$_2$·CH$_2$·CH=CH·CO·NHBu^i (III)

Me·CH$_2$·[CH=CH]$_3$·CH$_2$·CH=CH·CO·NHBu^i (IV)

H·[CH=CH]$_3$·CH$_2$·CH$_2$·CH$_2$·CH=CH·CO·NHBu^i (V)

Me·[CH=CH]$_3$·CH$_2$·CH$_2$·CH=CH·CO·NHBu^i (VI)

The geometrical stereochemistry of *neo*herculin can be partly, but not completely, settled. The C=C stretching vibration (1670 cm.$^{-1}$) of the αβ-double bond lies in a region characteristic of *trans*-αβ-unsaturated amides (1668—1675 cm.$^{-1}$), the corresponding *cis*-compounds having absorption at 1652—1660 cm.$^{-1}$. Five examples of each type are given in previous Parts of this series. The strong absorption at 993 cm.$^{-1}$ in the CH=CH out-of-plane deformation region of the infra-red is due to triene and the second, moderately strong peak in this region (970 cm.$^{-1}$) might be assigned to the *trans*-double bond αβ to the carboxyamide grouping (this usually appears at *ca.* 977 cm.$^{-1}$ and is absent in the *cis*-compound); however, the possibility of absorption in this region by the particular configuration of the triene present in *neo*herculin makes the assignment uncertain (α-elaeostearic and α-kamlolenic acid each have absorption at 991—993 and 967 cm.$^{-1}$. Absence of an absorption maximum of medium intensity at 818 cm.$^{-1}$ also agrees with an αβ-*trans*-linkage (see Parts I and II, *locc. cit.*). A maleic anhydride adduct was not formed by *neo*herculin at 100° and this suggests that there are not two contiguous *trans*-double bonds. The relatively low extinction coefficients in the ultra-violet (Table) also denote the presence of one or more *cis*-linkages. Nothing is known of the stereochemistry of affinin, but the report that it too does not give a maleic adduct (Acree, Jacobson, and Haller, *loc. cit.*) indicates that the diene system is not *trans-trans*.*

After removal of *neo*herculin, the mother-liquors from the extract still showed high insecticidal activity. By chromatography this fraction can be resolved into three groups of crude fractions. The main one shows high activity towards *Tenebrio molitor* and is a powerful sialogogue: the other two are innocuous. No pure compound has as yet been isolated from this main group. Spectroscopic results suggest that a polyene *iso*butylamide, possibly containing a conjugated triene system, is responsible for the activity and the material awaits further study.

The original observation that southern prickly ash bark contains an insecticidal substance was made by La Forge, Haller, and Sullivan (*J. Amer. Chem. Soc.*, 1942, **64**,

* Since this paper was submitted Jacobson (*J. Amer. Chem. Soc.*, 1954, **76**, 4606) has suggested that the αβ-linkage in affinin is *cis*, as a moderately strong band at 818 cm.$^{-1}$ disappears on stereomutation. The diene system is thought to be *cis-trans*, but its orientation is unknown.

187). Isolation of the active material, m. p. 59—60°, was claimed by Jacobson (*ibid.*, 1948, **70**, 4234) who named it herculin and gave it structure (VII). That this could not

$$Me{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i \quad \text{(VII)}$$

be so was demonstrated in Part I. From the description of the isolation and properties of herculin, it seems likely that herculin was crude *neo*herculin.

Experimental

Analyses and light absorption measurements (Hilger medium quartz instrument; solvent, ethanol) were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. I. Boston) laboratories of this Department.

Investigation of Southern Prickly Ash Bark.—Ground bark (6 kg.) was continuously extracted (cold Soxhlet-type apparatus) with light petroleum (b. p. 40—60°) for 32 hr. The extract was adjusted to 3 l. and agitated with nitromethane (300 ml.) to dissolve solids which had crystallised. The petroleum solution was then extracted with further nitromethane (2 × 300 ml.; 1 × 200 ml.; 3 × 100 ml.), and these green nitromethane extracts were united; the petroleum solution was then discarded. After removal of the nitromethane *in vacuo*, the residual oil was dissolved in ether (500 ml.) and washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water. This dried (Na_2SO_4) extract was evaporated and repeatedly extracted with boiling light petroleum (b. p. 60—80°; 10 × 100 ml.).

The remaining dark viscous liquid was first examined. Stirring it with hot ethanol gave an extract which yielded asarinin (6·05 g. after two crystallisations and treatment with charcoal; m. p. and mixed m. p. 121—122°). The residual oil deposited large crystals when set aside for 3 weeks; these were triturated with a little ethanol and filtered off. Crystallisation from light petroleum (b. p. 60—80°)–ethyl acetate and treatment with charcoal gave herclavin, m. p. 76°, in massive well-formed crystals (5·0 g.).

The light petroleum (b. p. 60—80°) extracts (1 l.) deposited an oil at 20° which yielded asarinin (2·3 g.) and herclavin (2·5 g.). When evaporated to 400 ml. and cooled to 0° (4 hr.) the solution deposited more oil which contained asarinin (3·15 g.) and herclavin (15 g.), together with a little impure *iso*butylamide (0·15 g.; characteristic pungency). After a further reduction of the volume to 200 ml. by distillation, almost pure asarinin (0·92 g.) crystallised. On filtration and storage at 0° (18 hr.) glistening plates of pure asarinin (2·96 g.) were deposited.

As nothing more crystallised after 6 hr. at 0°, cooling was continued with solid carbon dioxide–ethanol: after some delay, a gel separated which was filtered off with difficulty and roughly dried by being pressed on a porous plate (0·20 g.; m. p. 67—69°). Further cooling gave more gel which when treated as above gave rather sticky green flakes (1·30 g.; m.p. 61—63°). These two crops were crude *neo*herculin.

Prolonged cooling at −40° yielded no more solid and after 3 days at 0° only traces of asarinin (45 mg.) and herclavin (21 mg.) were produced. Repetition of the cooling to −40° gave a green impure waxy solid (340 mg.) with characteristic pungent taste; ultra-violet absorption max. at 227, 258, 269, 280 mμ ($E^{1\%}_{1cm.}$ 450, 900, 1050, 990) and infra-red absorption bands (cm.$^{-1}$) at, *inter alia*, 3302 s, 1741 w, 1668 ms, 1629 ms, 1570 m, 1039 w, 992 s, 969 m, 937 w, 929 w.

The light petroleum mother-liquors were then chromatographed on alumina, development being effected by acetone–light petroleum (b. p. 40—60°). A fast-running yellow band was followed by a wide green band. Eight fractions were taken, falling into three groups (the following abbreviations are used: s = strong, m = medium, w = weak, ms = medium-strong, i = inflexion. I% refers to the percentage of *Tenebrio molitor* immobilised 24 hr. after topical application of a 4% w/v solution in acetone): (*a*) Fraction 1; a yellow liquid (0·21 g.) depositing a few hair-like crystals at 0°, insecticidally inactive (*Tenebrio molitor*), with no pungent taste. Ultra-violet absorption max. at 227, 251, 258, 285 mμ ($E^{1\%}_{1cm.}$ 400, 160, 160, 210); infra-red absorption bands (cm.$^{-1}$) at 1735 m, 1616 w, 1040 s, 993 m, 948 i, 935 m. (no absorption at 3200—3400 cm.$^{-1}$). (*b*) Fractions 2—5 (5·0 g.), amber or yellow green, waxy or partly crystalline at 0°, unstable in air, highly insecticidally active (I% 92—96%), and possessing a burning taste and sialogogue effect. The following data relate to fraction 4 (1·52 g.): light absorption max. at 227, 269, 280 mμ ($E^{1\%}_{1cm.}$ 400, 1050, 780; infra-red absorption bands (cm.$^{-1}$) at 3302 s, 1672 ms, 1632 s, 1553 m, 1039 w, 992 s, 969 i, 922 w. (*c*) Fractions 6—8 (3·15 g.), yellow green, depositing fine crystals at 0°, insecticidally inactive, burning taste absent though bitter. The following data relate to fraction 6 (2·45 g.): light absorption max.

at 227, 251, 270, 280 mμ ($E^{1\%}_{1cm}$ 520, 160, 520, 660); infra-red absorption bands (cm.$^{-1}$) at 3374 (w and broad), 1655 ms, 1612 ms, 1511 ms, 1038 s, 1001 w, 976 m, 932 m.

Herclavin has light absorption max. at 223 and 280 mμ (ε 21,500 and 22,700) and infra-red absorption bands (cm.$^{-1}$) at *inter al.*, 1655 s, 1610 s, 1576 w, 1509 m, 1036 i, 1027 s, 991 ms, 982 s (no absorption at 3200—3400 cm.$^{-1}$). Asarinin has light absorption max. at 236 and 286 mμ (ε 9600 and 9600) and infra-red absorption bands (cm.$^{-1}$) at *inter al.*, 1255 s, 1247 m, 1225 w, 1192 m, 1179 m, 1100 m, 1074 s, 1050 w, 1036 s, 998 w, 986 w, 968 w, 959 m, 936 m, 928 s, 892 w, 881 m, 869 w, 836 w, 824 m, 809 m, 795 s, 786 w, 737 m (no absorption at 3200—3400 cm.$^{-1}$). Asarinin and herclavin are insecticidally inactive.

*neo*Herculin has been isolated from two specimens of bark, but a third gave little or none, although asarinin and herclavin were present as usual.

neo*Herculin*.—The crude material (above) formed neo*herculin* as colourless needles, m. p. 69—70°, from light petroleum (b. p. 40—60°) at 0° but tended to separate as a bulky gel which gave a hard pad when filtered off (Found: C, 77·3; H, 10·2; N, 5·7. $C_{16}H_{23}ON$ requires C, 77·65; H, 10·2; N, 5·65%). A Rast molecular-weight determination was not possible as the sample decomposed when fused with camphor. *neo*Herculin is soluble in most organic solvents: in air at 25° it becomes yellow and sticky, then forming a hard brown varnish. For light absorption data see Table. The infra-red absorption was closely similar to that of the slightly less pure material m. p. 63—65° mentioned in Part I, where the spectrum is given.

Hydrogenation of neo*Herculin*.—On microhydrogenation in glacial acetic acid with Adams catalyst *neo*herculin absorbed hydrogen equivalent to 3·75 (3·8, 3·75, 3·65) double bonds. In a preparative experiment, ethyl acetate was used as solvent (3·6 mols. absorbed). After separation of the catalyst and evaporation, *N-iso*butyldodecanamide, m. p. 53—54°, was isolated, undepressed by admixture with an authentic specimen (m. p. 53°). The saturated amide (11·6 mg.) was hydrolysed at 100° with concentrated hydrochloric acid (0·2 ml.) and ethanol (0·8 ml.) for 48 hr. The product was added to excess of 2N-sodium hydroxide and refluxed for 1 hr. Acidification and isolation in the usual way yielded the crude acid (4·8 mg.). This was chromatographed (Howard and Martin's technique, *Biochem. J.*, 1950, **46**, 532; cf. Part IV). The acid was eluted in the characteristic position for dodecanoic acid and contained less than 1·5% of decanoic acid. No acids of greater chain length were detected.

Action of Maleic Anhydride.—*neo*Herculin (25 mg.) was sealed with maleic anhydride (10 mg.) and benzene (0·2 ml.) in a nitrogen atmosphere. After heating periods of 2, 4 and 10 hr. at 100° no crystallisation could be induced by cooling. No crystals were obtained after 14 days at 0° and evaporation of the solvent gave only a resin.

Acid Hydrolysis of neo*Herculin*.—The amide (46 mg.) was heated at 120° for 60 hr. in a sealed tube with concentrated hydrochloric acid (0·3 ml.) and ethanol (0·5 ml.). The product was extracted with ether. Evaporation of the aqueous phase and extraction with ethyl acetate gave *iso*butylamine hydrochloride, m. p. 170°, in plates or needles (undepressed by authentic material, m. p. 173—174°). The chloroplatinate, prepared in ethanol, formed plates, m. p. 235° (decomp.); authentic *iso*butylamine chloroplatinate had m. p. 240°; admixture with the naturally derived specimen gave m. p. 235—240° but m. p.s are somewhat dependent on rate of heating.

Ozonolysis of neo*Herculin*.—Ozonised oxygen was passed through the amide (150 mg.), dissolved in glacial acetic acid (4 ml.), for 80 min. Zinc dust (1 g.) and water (40 ml.) were added and *ca.* 5 ml. of the mixture distilled into freshly prepared Brady's reagent. After 48 hr. the crude 2 : 4-dinitrophenylhydrazone was collected and boiled with benzene (100 ml.), cooled, and filtered. The benzene extract was chromatographed on alumina (10″ by 1″) and the faster-running zone eluted. Evaporation gave a yellow solid (94 mg.) which, when crystallised once from ethanol, had m. p. 159° (45 mg.). After two further crystallisations it formed shining yellow plates, m. p. 165° undepressed when mixed with acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 167°. Admixture with formaldehyde or propaldehyde 2 : 4-dinitrophenylhydrazone caused large depressions. A blank ozonisation experiment resulted in no precipitate being formed with Brady's reagent.

The author is indebted to Dr. M. Elliott and Mr. P. Needham for the insecticidal data relating to *Tenebrio molitor* mentioned in this and the succeeding three Parts. This arrangement was made through the kindness of Dr. C. Potter (Department of Insecticides and Fungicides, Rothamsted Experimental Station).

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Amides of Vegetable Origin. Part IV. The Nature of Pellitorine and Anacyclin.*

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Pellitorine, a crystalline insecticidal substance isolated from *Anacyclus pyrethrum* DC. roots and hitherto accepted as a pure compound, is shown to contain at least three substances. Hydrogenated pellitorine, when hydrolysed, gives a mixture resolvable by reversed-phase chromatography into decanoic, dodecanoic, and tetradecanoic acid. *N-iso*Butyldeca-*trans*-2 : *trans*-4-dienamide is a major component of pellitorine: the other components must have closely related structures. Since pellitorine constitutes only a small part of the insecticidal amide fraction of the roots, and since the activity is not concentrated in it, interest shifts back to the main mixture. A preliminary examination of this is reported.

A new crystalline polyunsaturated *iso*butylamide isolated from pellitory root and named anacyclin is not a sialogogue and has low insecticidal activity. On catalytic hydrogenation it absorbs six mols. of hydrogen, yielding *N-iso*butyltetradecanamide. By spectroscopical studies and oxidative degradation, anacyclin is shown to be *N-iso*butyltetradeca-*trans*-2 : *trans*-4-diene-8 : 10-diynamide (III).

On controlled catalytic hydrogenation, anacyclin is converted into a highly effective sialogogue and insecticide, *N-iso*butyltetradeca-*trans*-2 : *trans*-4 : *cis*-8 : *cis*-10-tetraenamide.

Pellitorine is a crystalline material (m. p. 72°) isolated, by a process involving solvent extraction and distillation, from the roots of a member of the Compositae, *Anacyclus Pyrethrum* DC. (Gulland and Hopton, *J.*, 1930, 6; for references to earlier investigations see Part II, Crombie, *J.*, 1952, 4338). Gulland and Hopton found that acidic hydrolysis yielded *iso*butylamine and that hydrogenation gave *N-iso*butyldecanamide, two mols. of hydrogen being absorbed. They therefore considered it to be an *N-iso*butyldecadienamide. Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366) claimed to have located the position of the two double bonds by permanganate degradation and proposed structure (I). In Part II

(I) $Pr^{n}\cdot CH{=}CH\cdot CH_2\cdot CH_2\cdot CH{=}CH\cdot CO\cdot NHBu^{t}$ $\quad$ $Me\cdot[CH_2]_4\cdot CH{=}CH\cdot CH{=}CH\cdot CO\cdot NHBu^{t}$ (II)

it was shown by synthesis that none of the four possible stereoisomers of structure (I) was pellitorine. The nature of this substance is now re-examined.

Three samples of pellitory root were investigated and crystalline pellitorine (m. p. 72—73°) was obtained from all. The yield of crude distilled material was 0·13—0·3% calculated on dry root but only about 5% of this could be obtained as crystalline material, m. p. 72°. Gulland and Hopton (*loc. cit.*) record a yield of 0·04% but do not make it clear if crude or crystalline material is referred to. Jacobson (*loc. cit.*) gave a crude yield of 0·14% but stated that 99% of this was then pellitorine of m. p. 72°; he has kindly supplied the author with a sample of his crude material. It now has m. p. 62° and gave pellitorine only after repeated crystallisations which resulted in much loss. In the present work, all experiments on pellitorine were carried out with material of m. p. 72—73°.

The ultra-violet light absorption data of pellitorine (Table I) indicate that a sorbic-type chromophore is present; in consonance with this, a maleic anhydride adduct (m. p. 192°) is formed readily. Microhydrogenation indicates two double bonds and this, when taken with the identification of the product as *N-iso*butyldecanamide by Gulland and Hopton (*loc. cit.*; cf. Jacobson, *J. Amer. Chem. Soc.*, 1950, **72**, 1489) leads to (II) as the structure of pellitorine. Further, the reaction with maleic anhydride indicates a *trans-trans*-configuration. However, synthetic *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide (Crombie, *Chem. and Ind.*, 1952, 1034; following paper) had m. p. 90°, though it did not

* Part III, preceding paper.

depress that of pellitorine. Its maleic anhydride adduct (m. p. 192°) also caused no marked depression with that from pellitorine. The infra-red spectra of the two dienamides were identical, except that pellitorine contained an additional weak band at 909 cm.$^{-1}$ (34 bands were common to the two spectra and had similar intensities). Both substances possessed moderately high toxicity to *Musca domestica* L. and both were sialogogues. Pellitorine is rather more than half, and *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide about a third, as toxic as the pyrethrins tested at the same concentration. Nevertheless, pellitorine was lethal to the grain insect *Tenebrio molitor* L. in concentrations in which the synthetic *trans-trans*-amide (II) was innocuous. Two explanations for the discrepancies are possible. Either pellitorine is one of the other three stereoisomers of (II) or it is not homogeneous.

The first possibility can be disposed of. In Part V (following paper), synthesis of all stereoisomers of (II) is described and all differ widely from pellitorine in physical, spectroscopical, and physiological properties. The second possibility must be examined.

Repetition of Gulland's hydrogenation experiment revealed that the products were incompletely solid. After purification, hydropellitorine specimens had m. p.s between 32° and 36°, either raised or slightly depressed by pure *N-iso*butyldecanamide (m. p. 37—38°). Furthermore, pellitorine itself tended to give slightly higher analytical figures for carbon and lower figures for nitrogen than are required for the amide (II). Hydropellitorine was hydrolysed with ethanolic hydrochloric acid in a sealed tube and the presence of an *iso*butylamine cleavage fragment confirmed. The acidic product was chromatographed, by Howard and Martin's reversed-phase technique (*Biochem. J.*, 1950, **46**, 532), and three fatty acids were detected and estimated (Table 1). Their chromatographic characteristics indicate their identities as decanoic, dodecanoic, and tetradecanoic acid, and in the case of a related extract (see below) this has been confirmed by isolation.

TABLE 1. *Components of pellitory root.*

			Ultra-violet light absorption				Component acids, chain lengths (%)				
	M. p.	H_2 no.[1]	$\lambda_{max.}$ (mμ)	$\lambda_{infl.}$[2] mμ	$E^{1\%}_{1\,cm.}$ (max.)	$E^{1\%}_{1\,cm.}$ (infl.)[2]	C_8	C_{10}	C_{12}	C_{14}	C_{16}
Me·[CH$_2$]$_4$·[CH=CH]$_2$·CO·NHBu^{t}[4]	90°	112	258	264	1330	1200	—	100	—	—	—
Fraction A	70	114[3]	258	265	1300	1200	0·5	58·5	26	14	1
Fraction B	46—48	105[3]	258	265	1120	1020	1	49	25	25·5	0·5
Pellitorine	72	107	258	264	1350	1300	—	67	23	10	—
Anacyclin	121	48	259	265	1240	1100	—	—	—	100	—

[1] Hydrogen number, defined as the weight of substance in g. which absorbs one mole of hydrogen (see Ogg and Cooper, *Analyt. Chem.*, 1949, **21**, 1400). Determinations were made on samples of 5—10 mg. [2] When a Unicam photoelectric instrument is used, only the maximum at 258 mμ is observed. [3] Mean figure. [4] Part V (following paper). (t = *trans*).

Pellitorine is thus a sharply melting mixture of at least three amides. The light-absorption extinction coefficients indicate that all three components probably contain a fully conjugated *trans-trans*-diene *iso*butylamide chromophore, and the infra-red data (Table 2) are in agreement. A major component is undoubtedly the amide (II), but micro-hydrogenation figures allow a minor component to have more than two double bonds. The latter may be the cause of the marked toxicity to *Tenebrio molitor*, because *N-iso*butyldodeca-*trans*-2 : *trans*-4-dienamide (Crombie and Shah, unpublished work) is inactive (3% in acetone), indicating that the effect is not merely due to increasing chain length of the alkyl substituent. The potency of pellitory extract before distillation is comparable with that of pellitorine towards *Tenebrio* and as the preparation of the latter material involves great losses, interest in it, now that it is known to be heterogeneous, has receded. A preliminary examination of whole pellitory extract has therefore been made.

The root extract, after purification by solvent partition, was chromatographed on alumina. Components readily eluted by light petroleum (b. p. 40—60°)–ether were not resolved and form a related group of waxy highly insecticidal sialogogues (0·11—0·22% yield). They can be subdivided by crystallisation from light petroleum, in which they are extremely soluble, into fraction A (less soluble, m. p. 70°) and fraction B (m. p. 46—48°).

The composition of the mixture of saturated stem acids of the A fraction resembles that of pellitorine more than the B fraction which is richer in tetradecanoic acid. The melting point of the fraction A is undepressed on admixture with pellitorine, and there seems little doubt that the latter is similar material obtained by a different method of isolation.

TABLE 2. *Infra-red bands (cm.$^{-1}$)* [3] *relating to the stereochemistry of pellitorine.*

	ν-NH		ν-C=O	ν-C=C$_I$	ν-C=C$_{II}$	δ'-[CH=CH]$_2$
Me·[CH$_2$]$_4$·[CH=CH]$_2$·CO·NHBu^i	3295	3075	1625	1654	1614	994 [2]
Pellitorine	3300	3070	1625	1655 [1]	1615 [1]	995 [1, 2]

[1] These bands are in the correct positions for a *trans-trans*-stereoisomer (see Part V). [2] No absorption near 960 cm.$^{-1}$ (nearest band 942 cm.$^{-1}$). A band there is characteristic of a *cis*-containing configuration (see Part V). [3] Paraffin mulls. (t = *trans*.)

Both fractions A and B readily yield diene adducts and give *iso*butylamine on hydrolysis; their ultra-violet and infra-red absorption data indicate that a fully conjugated *trans-trans*-diene *iso*butylamide chromophore enters into their structures. The B fraction is particularly effective insecticidally and as a sialogogue: it is more unstable than the A fraction or than pellitorine, though these may decompose to a gum during some weeks at 0°. Microhydrogenation, considered in relation to the stem acid composition, shows that amides containing more unsaturation than two double bonds must be present in the B fraction and, as remarked earlier, these may be highly effective insecticides.

Continued elution with ether gives, after purification, a new component, anacyclin, m. p. 121°. This is also encountered if the crude light petroleum extracts of pellitory root are set aside at 0°; because of its marked insolubility in this solvent, it may then crystallise. This insolubility makes it simple to ascertain that the above A and B fractions are quite free from anacyclin. Despite its unusual properties, the compound is an aliphatic *iso*butylamide and its constitution and stereochemistry are elucidated below. Anacyclin is very soluble in chloroform or carbon tetrachloride but, in contrast to pellitorine or the A and B fractions, is only slightly toxic towards *T. molitor* under the usual conditions of test. It is optically inactive.

Analysis and molecular-weight determination of anacyclin lead to the empirical formula $C_{18}H_{25}ON$. The infra-red spectrum shows it to be a monosubtituted amide (NH stretching, 3300, 3060; amide A carbonyl 1625; amide B 1544 cm.$^{-1}$), which contains αβ-conjugated diene unsaturation (1655 and 1612 cm.$^{-1}$ strong). On microhydrogenation in acetic acid six mols. of hydrogen were absorbed in the presence of a platinum catalyst. Similar results were obtained on a macro-scale with palladium–charcoal in ethyl acetate and the product, dodecahydroanacyclin (m. p. 66°) was isolated in excellent yield. This is a saturated monosubstituted amide (infra-red absorption). On hydrolysis with ethanolic hydrochloric acid it gave *iso*butylamine hydrochloride and tetradecanoic acid. Dodecahydroanacyclin must therefore be the previously undescribed *N-iso*butyltetradecanamide: this was confirmed by synthesis.

Hydrolysis of anacyclin itself also gave *iso*butylamine hydrochloride so the unsaturation must all be located in the chain of the acid. Ultra-violet light absorption indicates that two double bonds are conjugated with the amide grouping (Table 3). This leaves unsaturation equivalent to four mols. of hydrogen to be placed in the rest of the chain. No vinyl grouping is present (infra-red spectrum) and the ultra-violet absorption makes it possible to rule out any system of conjugated double bonds other than that mentioned.

Anacyclin readily forms a maleic anhydride adduct which, as expected, absorbs five mols. of hydrogen when catalytically hydrogenated. The adduct has been of great value in determining the nature and position of the remaining unsaturation. In this adduct the 2 : 4-dienamide-type of chromophore is totally eliminated and determination of the ultra-violet absorption spectrum reveals the low-intensity absorption characteristic of a conjugated diyne which is not quite pure: some 4% of enediyne is indicated (calculated from the ε data for deca-2-ene-4 : 6-diynol at 282·5 mμ, given in Table 3). Repeated crystallisations have so far failed to eliminate this. Examination of the spectrum of the maleic anhydride adduct of *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide showed that no

interference with the detection of the diyne system is caused by maleic adduct formation. Presence of the diyne system is confirmed by the infra-red spectrum of both anacyclin and its maleic anhydride adduct. In thick films a doublet is found in the C≡C stretching region (Table 4). These vibrations are weak and barely detectable in paraffin mulls of the concentration and thickness generally employed in work on amides. Allenic vibrations could not be detected.

TABLE 3. *Ultra-violet light absorption (mμ) of anacyclin and related compounds.*

Anacyclin [1]	λ 230, ε 10,000; $\lambda_{max.}$ 259, ε 33,500					
Tetrahydroanacyclin [1]	λ 230, ε 24,000; $\lambda_{max.}$ 259, ε 30,500					
$Me[CH_2]_4 \cdot CH{=}CH \cdot CH{=}CH \cdot CO \cdot NHBu^i$ [1]	$\lambda_{max.}$ 259, ε 29,500					
Anacyclin maleic anhydride adduct	$\lambda_{max.}$	227	237	252	266	281
	ε	1850	1300	1100	1000	850
$Me \cdot [CH_2]_2 \cdot C{\equiv}C \cdot C{\equiv}C \cdot [CH_2]_9 \cdot Me$ [2]	$\lambda_{max.}$	228	239·5	254	—	—
	ε	440	390	240		
$CH_2{=}CH \cdot [CH_2]_4 \cdot C{\equiv}C \cdot C{\equiv}C \cdot [CH_2]_7 \cdot CO \cdot NHR'$ [3, 4]	$\lambda_{max.}$	227	238	251	—	—
	ε	640	445	180		
$Me \cdot [CH_2]_2 \cdot C{\equiv}C \cdot C{\equiv}C \cdot CH{=}CH \cdot CH_2 \cdot OH$ [5]	$\lambda_{max.}$	—	239·5	252	266·5	282·5
	ε	—	7300	14,600	21,850	19,440

[1] An inflexion at ~265 mμ is detectable. [2] Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998. [3] Black and Weedon, *J.*, 1953, 1785. [4] R = $CH_2 \cdot CH_2 \cdot OH$. [5] Bruun, Haug, and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 850.

TABLE 4. *Acetylene stretching frequencies (cm.$^{-1}$).*

Anacyclin [1]	2233 w	2206 vw
,, maleic adduct [1]	2243 w	2208 vw
$Me \cdot [CH_2]_2 \cdot C{\equiv}C \cdot C{\equiv}C \cdot [CH_2]_8 \cdot CO_2R$ [1, 2]	2253 w	2228 w, 2203 vw
$C_5H_{11} \cdot C{\equiv}C \cdot C{\equiv}C \cdot CO_2Me$ [3]	2251 s	2224 m
$C_5H_{11} \cdot C{\equiv}C \cdot CH{=}CH \cdot CO_2Et$ [3] (t = *trans*.)	—	2212 s

[1] Paraffin mulls. [2] R = *p*-$C_6H_4Br \cdot CO \cdot CH_2$. The author is grateful to Dr. B. C. L. Weedon for this sample. [3] Part V, liquid film.

The conjugated diyne system must be situated between $C_{(7)}$ and $C_{(13)}$ and its position was found by oxidative degradation. Ozonolysis caused resinification but permanganate degradation proved to be satisfactory. *N-iso*Butyloxamic acid, succinic acid, and a derivative of butyric acid were isolated. The presence of a diyne system makes intelligible the insolubility in light petroleum and the tendency to become pink in light (cf. Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998). On alkali isomerisation, the 259-mμ maximum of anacyclin disappeared and was replaced by a new maximum at 302 mμ. This wave-length, however, is rather short for a conjugated yne-trieneamide chromophore such as might be expected to develop under these conditions.

Three pieces of evidence show that the 2 : 4-diene system has the *trans-trans*-configuration. First, the ease of formation of a maleic adduct is characteristic, and, secondly, the infra-red trace shows only one peak at 996 cm.$^{-1}$ without a second in the 960—965 cm.$^{-1}$

$$Me \cdot [CH_2]_2 \cdot C{\equiv}C \cdot C{\equiv}C \cdot CH_2 \cdot CH_2 \cdot CH{=}CH \cdot CH{=}CH \cdot CO \cdot NHBu^i \quad \text{(III)}$$

region (the nearest is at 943 cm.$^{-1}$). Finally the two C≡C stretching bands (vibrational interaction) fall in the expected positions (values given above; see Part V for a full examination of these questions). Anacyclin is, therefore, *N-iso*butyltetradeca-*trans*-2 : *trans*-4-diene-8 : 10-diynamide (III).

In recent years numerous acetylenic compounds have been found in a number of flowering plants and fungi: in particular, straight chain conjugated enyne esters have been obtained from the Compositae family to which *Anacyclus pyrethrum* belongs (Williams, Smirnow, and Goljmow, *J. Gen. Chem., U.S.S.R.*, 1935, **5**, 1195; Sörensen and Stene, *Annalen*, 1941, **549**, 80; Holman and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 416; Stavolt and Sörensen, *ibid.*, pp. 1567, 1575; Baalsrud, Holme, Nestvold, Pliva, Sörensen, and Sörensen, *ibid.*, 1952, **6**, 883; Christiansen and Sörensen, *ibid.*, p. 893). The C_{18} fatty acid

erythrogenic acid obtained from the fruit kernel oil of *Ongokea Gore* Engler contains, like anacyclin, an isolated diyne linkage, though it belongs to another family (Castille, *Annalen*, 1940, **543**, 104; Steger and van Loon, *Rec. Trav. chim.*, 1940, **59**, 1156; Armitage *et al.*, *loc. cit.*; Black and Weedon, *J.*, 1953, 1785). It too tends to be contaminated with small amounts of material having a conjugated enediyne chromophore. An interesting feature of the structure of anacyclin is the dimethylene bridge between two unsaturated systems. This is characteristic of various insecticidal *iso*butylamides such as *neo*herculin (preceding paper), affinin (Acree, Jacobson, and Haller, *J. Org. Chem.*, 1945, **10**, 236, 449), scabrin (Jacobson, *J. Amer. Chem. Soc.*, 1951, **73**, 100), and sanshoöl I and II (Aihiara, *J. Pharm. Soc. Japan*, 1950, **70**, 43, 47). The system ·CH=CH·CH_2·CH_2·CH=CH· is also found in certain fish oils.

Existing evidence (Part III and above) suggests that unsaturation conjugated with the *iso*butylamide linkage is all-*trans* in at least some of the natural insecticidally active compounds of this class. On the other hand, *cis*-containing arrangements are desirable for "internal" unsaturation not conjugated with the amide grouping (Part III). Further, synthetical studies (Part V) show that, for the system

$$CH_3\cdot[CH_2]_4\cdot CH{=}CH\cdot CH{=}CH\cdot CO\cdot NHBu^i,$$

the *trans*-2 : *trans*-4- is ten times more active than the *trans*-2 : *cis*-4-compound towards *Musca domestica*. Anacyclin was therefore partially hydrogenated with lead–quinoline poisoned catalyst (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) until two mols. of hydrogen had been absorbed. The catalyst is largely selective and stereospecific for the hydrogenation of a diyne to a *cis-cis*-diene system (see Part V) so the product is formulated as *N-iso*butyltetradeca-*trans*-2 : *trans*-4 : *cis*-8 : *cis*-10-tetraenamide. It was not further purified, but the light absorption agrees with this structure, ε at 230 mμ having increased by 14,000 (Table 3) because the weakly absorbing diyne has been replaced by a *cis-cis*-diene chromophore. This new compound was very soluble in light petroleum and had strong sialogogue effect and insecticidal activity towards *Tenebrio molitor*. Like herculin and the fractions A and B (p. 1005) it rapidly deteriorated to a brown gum. The complete structure *and* the stereochemistry of an *iso*butylamide with high activity towards *Tenebrio* are thus known for the first time. It is conceivable that such a compound, or a stereoisomer about the 8 : 10-double bonds, might account for the *Tenebrio* activity of the fractions A and B.

Experimental

Microanalyses were carried out in the microanalytical laboratories (Mr. F. H. Oliver) and ultra-violet light absorption data measured in the spectrographic laboratories (Mrs. I. Boston) of Imperial College. The latter data were obtained with a Hilger medium quartz instrument and absolute ethanol as solvent.

Examination of Pellitory Root.—Ground root (8 kg.) was continuously extracted with light petroleum (b. p. 40—60°) in a large Soxhlet-type apparatus. When the extract was set aside for 2 weeks at 0° (vol., 1·5 l.), a yellow oil separated, together with crystals (1·1 g.; m. p. 109°). Five recrystallisations of the latter, from light petroleum (b. p. 40—60°) containing a little chloroform or carbon tetrachloride, gave anacyclin as white needles, m. p. 121°.

The main light petroleum solution was concentrated to 700 ml. and extracted with nitromethane (4 × 250; 5 × 100 ml.). These extracts were concentrated (500 ml.) and cooled at 0° for some days. Solid (2·6 g.), m. p. 58—62°, was deposited which from its odour, taste, and appearance was similar to the A and B mixtures described below. It was returned to the nitromethane solution, and the solvent removed *in vacuo*. The pale yellow residue was dissolved in ether and washed with 2N-hydrochloric acid, and then with water. After drying and evaporation of the ether, a cream-coloured waxy solid (15·6 g., 0·195%) remained [absorption max. at 258; inflexion at 266 mμ ($E^{1\%}_{1cm}$ 910, 870)]. This is referred to below as "purified pellitory extract."

Root from a different source (3·63 kg.) was ground immediately before extraction. The extracts deposited 2·6 g. of crude anacyclin, and purified pellitory extract was obtained in 0·37% yield.

Pellitorine.—Purified pellitory extract (4·2 g.) was distilled (b. p. 158—195°/0·07 mm.). The pale yellow distillate (3·45 g.), collected as one fraction, crystallised as a waxy mass of

needles (m. p. 48—53°) (Found: C, 75·75; H, 11·05; N, 5·05%; H_2 no., 114). Light absorption: $\lambda_{max.}$ 258, $\lambda_{infl.}$ 266 mμ ($E^{1\%}_{1cm.}$ 1070, 1020). This was crystallised from light petroleum (b. p. 40—60°; *ca.* 5 ml.) and after three days at 0° the crystals were collected by filtration at 0°. Three further crops were obtained, after concentration, by similar slow crystallisations. This product (300 mg.; m. p. 63—66°) was twice crystallised from light petroleum in long silky needles and then melted sharply at 72° (184 mg.) (Found: C, 75·55; H, 11·1; N, 6·0. $C_{14}H_{25}ON$ requires C, 75·25; H, 11·3; N, 6·25%; H_2 no., 112. $C_{16}H_{29}ON$ requires C, 76·5; H, 11·65; N, 5·55%; H_2 no., 126). For other data see Table 1. A specimen obtained from another batch of root had m. p. 73° (Found: C, 75·8, 75·9; H, 11·15, 11·20; N, 5·65, 6·1%. H_2 no., 111) and light absorption $\lambda_{max.}$ 256, $\lambda_{infl.}$ 264 mμ ($E^{1\%}_{1cm.}$ 1450; 1350).

A specimen received from Dr. Jacobson had m. p. 62—63°, raised by three crystallisations (with much loss) to 73° [light absorption: $\lambda_{max.}$ 257, $\lambda_{infl.}$ 265 mμ ($E^{1\%}_{1cm.}$ 1350, 1300)], undepressed on admixture with the pellitorine specimens described above.

Pellitorine is a potent sialogogue. A 3·1% solution in acetone, when tested by topical application of measured drops under defined conditions, against adult *Tenebrio molitor* L., caused 45% immobilisation after 24 hr. (see Report of Rothamsted Exp. Station, 1952, p. 103). It formed a maleic anhydride *adduct* (Found: C, 67·9; H, 8·9. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5. $C_{20}H_{31}O_4N$ requires C, 68·7; H, 8·95%), which crystallised from benzene in needles, m. p. 192° (unsharp), not depressed on admixture with the maleic anhydride adduct of *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide.

Hydrogenation of Pellitorine.—The material was completely hydrogenated in ethyl acetate in presence of palladium–calcium carbonate. After filtration and evaporation *in vacuo*, the product was semisolid at 25°; after being pressed on a porous tile it had m. p. 34—36°, depressed to 31—32° if admixed with pure *N-iso*butyldecanamide (m. p. 37—38°). Another specimen had m. p. 32°, unaltered by admixture with *N-iso*butyldecanamide.

Hydrolysis of Hydropellitorine.—Pellitorine (92 mg.) was hydrogenated as described above and the hydropellitorine heated at 100° for 2 days with ethanol (2 ml.) and concentrated hydrochloric acid (0·7 ml.) in a sealed tube. The mixture was then diluted with water and extracted with ether. Evaporation of the aqueous phase and recrystallisations from ethyl acetate gave *iso*butylamine hydrochloride, m. p. 171—172° undepressed by an authentic specimen of m. p. 174°. The ethereal extract was evaporated and hydrolysed by heating it under reflux with 2N-sodium hydroxide. Neutral material was removed by ether-extraction, and the acids, liberated by acidification, were isolated in the usual way. After removal of traces of ether at 0·02 mm., the acidic hydrolysis product was chromatographed on a column (30 cm. × 12 mm.) of water-repellent kieselguhr impregnated with liquid paraffin (B.P.) and eluted with solutions of acetone in water (successively 35%, 45%, 50%, 60%, 70% of acetone). Three components were separated (in the 45%, 50%, and 60% solutions): these correspond to decanoic, dodecanoic, and tetradecanoic acid, as shown by chromatography of a standard mixture (see also the isolation below). The progress of the chromatogram and composition of the mixture was followed by microtitration of three hundred successive 2-ml. portions of eluant to bromothymol-blue (see Table 1).

Chromatography of Purified Pellitory Extract.—The extract (11·2 g.) was dissolved in 5 : 1 light petroleum (b. p. 40—60°) and ether, and the brown solution chromatographed on alumina (30 × 3 cm.). After elimination of a trace of a yellowish substance, the material eluted by the above solvent (650 ml.), and then by light petroleum (b. p. 40—60°) and ether (1 : 1; 500 ml.), was collected in five fractions (total 6·14 gm.). These are referred to as X. Further elution with pure ether (750 ml.) gave crude orange material (3·95 gm.) differing from the above in its low sialogogue effect, low insecticidal effectiveness (*Tenebrio*), and low solubility in light petroleum. The latter crude fractions were repeatedly extracted with light petroleum (b. p. 60—80°), and the extracted solid (1·4 g.) was crystallised from this solvent containing a little chloroform to give anacyclin, m. p. 121° (0·3 g.). Resinous material remained. Further elution with ether–ethanol (4 : 1) gave a clear brown resin with a characteristic odour which gave no crystals when extracted with light petroleum (b. p. 60—80°).

Examination of the Material X.—The fractions X were white or pale yellow waxy solids of m. p. 38—55°, extremely soluble in light petroleum (b. p. 40—60°), and highly potent insecticides and sialogogues. A specimen of the united fractions (m. p. 49°) caused immobilisation of 96% of the insects after 24 hr., when applied to *Tenebrio* at a concentration of 3·15% (in acetone). They were very unstable and changed to dark resins in a few days at 0° in stoppered tubes under nitrogen. They are best kept in solution in light petroleum or ether. On their dissolution in a small quantity of light petroleum (10 ml./g.; b. p. 40—60°) and storage for 3 days at

0°, sheaves of needles were deposited. The material X (6·14 g.) gave 0·61 g. (m. p. 70°). This material is termed A (0·01% calc. on dried root), and the petroleum-soluble fraction B (0·096%).

Fraction A.—Admixture with pellitorine (m. p. 72—73°) did not depress the m. p. (Found: C, 75·0, 75·75; H, 11·5, 11·2; N, 6·05, 6·0%. H_2 no., 112, 116). Light absorption: $\lambda_{max.}$ 258, $\lambda_{infl.}$ 265 mμ ($E^{1\%}_{1\,cm.}$ 1400, 1300) (see also Table 1). The material A (139 mg.) was hydrogenated and hydrolysed with alcoholic hydrochloric acid as described under pellitorine. The hydrochloride of the basic fraction (57 mg.), after crystallisations from ethyl acetate, had m. p. 171°, undepressed on admixture with *iso*butylamine hydrochloride, m. p. 173°. The acids (used, 40·3 mg.) were subjected to reversed-phase chromatography and the approximate composition is given in the Table.

Fraction B.—This was a pale yellow waxy solid, m. p. 46—48° (Found: C, 75·65, 76·1; H, 11·25, 11·2; N, 5·5, 5·65%; H_2 no., 108, 102). Light absorption: $\lambda_{max.}$ 258, $\lambda_{infl.}$ 265 mμ ($E^{1\%}_{1\,cm.}$ 1100, 1000). See also Table 1. The material B (570 mg.) was hydrogenated, hydrolysed with ethanolic hydrochloric acid, and worked up as above. The crude amine hydrochloride (125 mg.) was thrice crystallised from ethyl acetate, forming plates, m. p. 170°, undepressed by authentic *iso*butylamine hydrochloride. The solid acids, when analysed by the chromatographic procedure, had the composition given in Table 1.

In an earlier experiment, a fraction X (m. p. 48—50°) [Found: C, 76·35; H, 11·3; N, 5·45%; H_2 no., 118. Light absorption: $\lambda_{max.}$ 258, $\lambda_{infl.}$ 264 mμ ($E^{1\%}_{1\,cm.}$ 1070, 920)] was hydrogenated (the product had m. p. 44—49°) and hydrolysed, and the acids (Found: C, 70·65; H, 11·95%; equiv., 190) were chromatographed. The fundamental acid composition was decanoic 40%, dodecanoic 33%, and tetradecanoic 27%. Solutions of the first two bands from the chromatogram were separately evaporated, and acidified, and the acid was collected with ether. Indicator (bromothymol-blue), which contaminated the acid, was removed by distilled water and the acid converted into its *p*-bromophenacyl ester. The derivative from the first acid was *p*-bromophenacyl decanoate, m. p. and mixed m. p. 65·5° (shining plates from ethanol). The second fraction gave *p*-bromophenacyl dodecanoate, m. p. and mixed m. p. 72°, markedly depressed by the derivatives of decanoic and tetradecanoic acid. The presence of tetradecanoic acid was established by distillation of the crude mixture of saturated acids (260 mg.) isolated by hydrogenation and hydrolysis of fraction X (540 mg.). After elimination of material, b. p. 118—120°/0·2 mm., n_D^{25} 1·4372, the temperature rose to 132° and a fraction was collected which solidified in the receiver (63 mg.) and, crystallised three times from ethanol–water, had m. p. 55—56°, undepressed by tetradecanoic acid.

Isolation of Anacyclin.—*Anacyclin* is deposited from light petroleum (b. p. 40—60°) extracts of pellitory root when set aside at 0°. The remainder of the material may be isolated from the extract, after partition with nitromethane, by chromatography (see above). Total yields are 0·03—0·07% based on dry root. Anacyclin is sparingly soluble in light petroleum: when repeatedly crystallised from this (b. p. 60—80°) it had m. p. 116° but the m. p. could be raised to 121° by further crystallisations from light petroleum containing a little chloroform, carbon tetrachloride, or ethyl acetate [Found: C, 79·7, 79·85, 79·5; H, 9·6, 9·5, 9·2; N, 5·4; 5·5, 5·2%; *M* (Rast), 284. $C_{18}H_{33}ON$ requires C, 79·7; H, 9·3; N, 5·15%; *M*, 271·4. Microhydrogenation no., 47·6, 47·7, 46·7, equiv. to 5·7, 5·7, 5·8 H_2]. For ultra-violet light absorption see Table 2. The substance crystallises in white needles but in stoppered tubes at 0° it becomes yellow in a few days, and the m. p. falls. The crystals are conveniently stored under a layer of light petroleum at 0°. When dried at 25° or 70° in light, a specimen became salmon pink (even at 0·5 mm.). A 3% solution in acetone, when tested against *Tenebrio molitor* by the measured-drop technique, caused only 10% mortality. This may be a reflexion of its low lipoid solubility.

Dodecahydroanacyclin.—Anacyclin (332 mg.) was completely hydrogenated in methyl acetate solution in presence of 5% palladium and charcoal (200 mg.). (Absorption of hydrogen 166 ml. at N.T.P.; calc. for $6H_2$, 165 ml.) Kieselguhr was added, the catalyst removed by filtration and the solution concentrated. Colourless needles (267 mg.), m. p. 66°, of the *decahydro-compound* were deposited [Found: C, 76·5; H, 13·5; N, 4·9%; *M* (Rast) 269. $C_{18}H_{37}ON$ requires C, 76·25; H, 13·15; N, 4·95%; *M*, 283·5]. The infra-red spectrum (paraffin mull) showed bands at 3310, 3075 (NH stretching), 1641 (amide A C=O) and 1548 (amide B) cm.$^{-1}$.

Hydrolysis of Dodecahydroanacyclin.—The dodecahydro-compound (210 mg.) was heated at 80—105° in a sealed tube with ethanol (8 ml.) and concentrated hydrochloric acid (2 ml.) for 3 days, then diluted with water and extracted with ether. Evaporation of the aqueous phase gave *iso*butylamine hydrochloride (88 mg.) which when crystallised from ethyl acetate had m. p. 173—174°, undepressed by an authentic specimen m. p. 174—175° (Found: Cl, 32·25. Calc. for $C_4H_{12}NCl$: Cl, 32·25%). The ethereal extract was evaporated and acidic material extracted

with 2N-sodium hydroxide. Liberation with 2N-sulphuric acid gave crude tetradecanoic acid (73 mg.) which was converted into its *p*-bromophenacyl ester, plates (from ethanol), m. p. and mixed m. p. 80°.

N-iso*Butyltetradecanamide*.—This was prepared in the usual way from tetradecanoyl chloride and *iso*butylamine and crystallised from ethyl acetate in needles, m. p. 66°. When admixed with dodecahydroanacyclin, there was no depression of m. p.

Maleic Anhydride Adduct of Anacyclin.—Anacyclin (90 mg.), maleic anhydride (10 mg.), and benzene (0·6 ml.) were heated together for 18 hr. in a sealed tube at 80—100°. The material (77 mg.) which crystallised from the brown solution on cooling was washed with cold benzene and then crystallised from this solvent, after treatment with charcoal. The *adduct* was obtained in needles, m. p. 193° (decomp.) (Found: C, 71·7, 70·5; H, 7·6, 7·35. $C_{33}H_{47}O_4N$ requires C, 71·5; H, 7·35%. Microhydrogenation no., 82·1, equiv. to 4·5H_2). For light absorption, see Table 2.

Tetrahydroanacyclin.—Anacyclin (99·8 mg.) was stirred, in ethyl acetate solution containing a drop of quinoline, with lead-poisoned palladium catalyst (200 mg.; Lindlar, *loc. cit.*) under hydrogen, until 15·88 ml. (N.T.P.) were absorbed (Calc. for 2H_2: 16·5 ml.). After filtration, solvent was evaporated *in vacuo* and the residue dissolved in ether and washed with dilute sulphuric acid and then water. The solution was dried and evaporated; the unpurified residue, heated at 100°/1 mm., crystallised on cooling as rosettes of waxy needles, m. p. 40°. This material was used for the light absorption determination. It was a strong sialogogue and, when tested against *Tenebrio* as a 3% solution in acetone, caused 100% immobilisation.

Oxidation of Anacyclin.—Potassium permanganate (1·4 g.) was added a little at a time to anacyclin (260 mg.), suspended in water (25 ml.) and acetone (5 ml.) at 50°. All was decolourised and the precipitated manganese dioxide was removed and well washed with hot water. The solution was acidified and steam-distilled, 220 ml. being collected. The distillate required 14·0 ml. of 0·1N-alkali for neutralisation. It was then again acidified and steam-distilled, 20-ml. portions being collected and titrated. The first five, containing the most volatile material, required 7·6 ml. of 0·1N-alkali (the theor. yield of butyric acid would require 9·6 ml.). After concentration, this gave an *S*-benzylthiuronium salt, m. p. 145°. Donleavy (*J. Amer. Chem. Soc.*, 1936, **58**, 1004) gives m. p. 146° for the derivative of *n*-butyric acid. However, an authentic specimen was found to give values as high as 153° depending on the rate of heating. Berger (*Acta Chem. Scand.*, 1954, **8**, 427) has recently commented on the similar behaviour of a range of *S*-benzylthiuronium salts and gives m. p. values from 144° to 150° for the butyric acid derivative. The m. p. of the derivative of the oxidation product was undepressed on admixture with that of *n*-butyric acid, but when admixed with *S*-benzylthiuronium propionate (m. p. 154°) gave a substantial depression.

The solution of non-steam volatile oxidation products (75 ml.) was continuously extracted with ether for 4 days. The ether was evaporated, leaving a brown mass of crystals. This was extracted with boiling light petroleum (4 × 30 ml.; b. p. 40—60°). Evaporation of the extract and recrystallisation from the same solvent gave *N-iso*butyloxamic acid, m. p. 107°, undepressed by an authentic specimen (m. p. 108°; cf. Malbot, *Compt. rend.*, 1887, **104**, 229) prepared by oxidation of *N-iso*butylsorbamide by the above procedure.

The residue, after extraction with light petroleum, was fractionally sublimed at 0·02 mm. and the residue remaining in the apparatus (crystals and resin) was thrice crystallised from ethyl acetate in needles, m. p. 185°, undepressed on admixture with authentic succinic acid (m. p. 186°) but heavily depressed by oxalic acid [m. p. 181° (decomp.)].

Alkaline Treatment of Anacyclin.—The amide (20 mg.) was refluxed for 15 min. with 25% aqueous potassium hydroxide. Slight darkening occurred. The cooled solution was extracted with ether, and the extracts were evaporated. Crystallisation from light petroleum (b. p. 40—60°)–ether gave unchanged anacyclin (mixed m. p.).

Anacyclin (9·8 mg.) was sealed in a glass tube with 20% potassium hydroxide in ethylene glycol (1 ml.) and heated at 180° for 20 min. A brown colour developed. The solution was diluted with ethanol, and an aliquot part used for light absorption measurements: $\lambda_{max.}$ 302 mμ ($E^{1\%}_{1\,cm.}$ 350). A blank determination was carried out.

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Amides of Vegetable Origin. Part V. Stereochemistry of Conjugated Dienes.*

By L. Crombie.

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Essentially stereospecific syntheses of the four methyl deca-2 : 4-dienoates are described. This is the first preparation of a compound

R·CH=CH·CH=CH·R′

in all four forms. The four forms of the corresponding acids, *iso*butylamides, *p*-bromophenacyl esters, and *S*-benzylthiuronium salts are also described, together with the deca-2 : 4-dienols obtained by lithium aluminium hydride reduction. *N-iso*Butyldeca-*trans*-2 : *trans*-4-dienamide, a component of pellitorine, is one of the amides prepared. Methyl stillingate, from stillingia oil, is reinvestigated; it is identical with synthetic methyl deca-*trans*-2 : *cis*-4-dienoate.

The steric stability, properties, and physiological action of the compounds are discussed. Their ultra-violet spectra possess characteristic features, and regularities in the infra-red spectra, particularly in the C=C stretching region and the unsaturated C–H out-of-plane deformation region, are observed. An explanation for the spectroscopical results is suggested.

During structural and synthetical investigations of certain natural lipids (aliphatic polyene *iso*butylamides † of plant origin and acids derived from natural fats) at present in progress in these laboratories, the paucity of fundamental information on geometrical isomerism in conjugated systems has hindered progress. An investigation of the systems ·CH=CH·CH=CH· and ·CH=CH·CH=CH·CO_2R is described in this communication. The four theoretically possible stereoisomers were prepared by methods which are largely or entirely stereospecific and are believed to be generally applicable to compounds of a similar type. The geometrical isomers have been examined in the hope of finding satisfactory methods for diagnosis of configuration in stereochemically unknown systems and some progress has been made, particularly by spectroscopical methods.

In Parts I and II (Crombie, *J.*, 1952, 2997, 4338), *trans*-2 : *trans*-6-, *trans*-2 : *cis*-6- and *cis*-2 : *trans*-6-stereoisomers of the amide (I), together with *trans*-2 : *trans*-8- and *cis*-2 : *trans*-8-stereoisomers of (II) were prepared. The remaining stereoisomers of these amides were already known, so these have become the first two cases in which, for a structure of the non-conjugated type (III; R ≠ R′), all four isomers are available.

(I) Me·$[CH_2]_3$·CH=CH·CH_2·CH_2·CH=CH·CO·NHBu^i

(II) Me·$[CH_2]_3$·CH=CH·CH_2·CH_2·CH_2·CH_2·CH=CH·CO·NHBu^i

(III) R·CH=CH·$[CH_2]_n$·CH=CH·R′

R·CH=CH·CH=CH·R′ (IV)

Me·$[CH_2]_4$·CH=CH·CH=CH·CO_2H (V)

Me·$[CH_2]_4$·CH=CH·CH=CH·CH_2·OH (VI)

The three theoretically possible isomers of the conjugated system (IV; R = R′) are known for 1 : 4-diphenylbutadiene (for references see Pinckard, Wille, and Zechmeister, *J. Amer. Chem. Soc.*, 1948, **70**, 1938) and muconic acid (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235; cf. also αα′-dimethylmuconic acid, Elvidge, Linstead, and Smith, *J.*, 1952, 1026). However, for the general type (IV; R ≠ R′) the four theoretically possible geometrical isomers have not hitherto been synthesised. In the case of sorbic acid, only two isomers (*trans*-2 : *trans*-4 and *cis*-2 : *trans*-4) are known * (Eisner, Elvidge, and Linstead, *J.*, 1953, 1372). Syntheses of three of the stereoisomers of piperic acid are claimed (Ott and Eichler, *Ber.*, 1922, **55**, 2653; Lohaus, *J. pr. Chem.*, 1928, **119**, 235;

* Part IV, preceding paper.

† Little attention has been paid to the classification of this group of amides but occasional references are to be found in treatises on the alkaloids (*e.g.*, Winterstein and Trier, "Die Alkaloide," Borntraeger, 1931, p. 159; Henry, "The Plant Alkaloids," Churchill, 1942, p. 2; Manske and Holmes, "The Alkaloids," Academic Press, 1950, Vol. I, p. 171). They have no basic properties and are more satisfactorily considered in the lipid group.

Annalen, 1934, **513**, 219; 1936, **525**, 312; Lohaus and Gall, *ibid.*, 1935, **517**, 278) but re-investigation of some aspects of this subject seems desirable.

The compounds of type (IV; R ≠ R') selected for detailed examination in the present investigation are the deca-2 : 4-dienoic acids (V) and related compounds (methyl esters, *iso*butylamides, and standard crystalline derivatives). In addition the four stereoisomers of the deca-2 : 4-dienols have been prepared and examined. This choice was made because a number of natural *iso*butylamides have the structural feature $\cdot CH_2 \cdot CH{=}CH \cdot CH{=}CH \cdot CO \cdot NHBu^i$ or $R \cdot CH{=}CH \cdot CH{=}CH \cdot CH_2 \cdot$, *e.g.*, anacyclin (preceding paper), the sanshoöls (Aihara, *J. Pharm. Soc. Japan*, 1950, **70**, 43, 47), and affinin (Acree, Jacobson, and Haller, *J. Org. Chem.*, 1945, **10**, 236, 449; 1947, **12**, 731). A major component of the pellitorine complex (preceding paper) is *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide and its synthesis is described below. During the investigation, a stereospecific synthesis of stillingic acid, which occurs as a glyceride in stillingia oil, was effected.

Synthesis of the Stereoisomeric Deca-2 : 4-dienoic Acids and Deca-2 : 4-dienols.—At the outset of this investigation none of the deca-2 : 4-dienoic acids or their derivatives had been prepared. In connection with the nature of pellitorine, an interim account of the *trans*-2 : *trans*-4-acid and its *iso*butylamide was given (Crombie, *Chem. and Ind.*, 1952, 1034). A synthesis of this compound by a slightly different route has been reported by Jacobson (*J. Amer. Chem. Soc.*, 1953, **75**, 2584).

Deca-trans-2 : trans-4-*dienoic acid.* This was prepared from hept-1-yne. Heptynylmagnesium bromide was converted into 1 : 1-diethoxyoct-2-yne (VIII) by treatment with ethyl orthoformate. Semihydrogenation with palladium–calcium carbonate or –barium sulphate (palladium–charcoal is less selective) gave 1 : 1-diethoxyoct-2-ene (IX; presumably *cis*) which on acidic hydrolysis gave *trans*-oct-2-enal. The complete stereochemical inversion is induced by the acidic conditions (Raphael and Sondheimer, *J.*, 1951, 2693; Crombie, Harper, and Thompson, *J.*, 1951, 2906; Crombie and Tayler, unpublished work). *trans*-Octenal had the expected light absorption, gave a 2 : 4-dinitrophenylhydrazone, and when condensed with malonic acid in the presence of pyridine yielded deca-*trans*-2 : *trans*-4-dienoic acid. (For evidence that a *trans*-linkage is formed under Doebner conditions see Crombie, *Quart. Reviews*, 1952, **6**, 101, and Part I.) It was characterised, as were the other stereoisomers described below, by its *p*-bromophenacyl ester and *S*-benzylthiuronium salt. Spectroscopical and other data are discussed later.

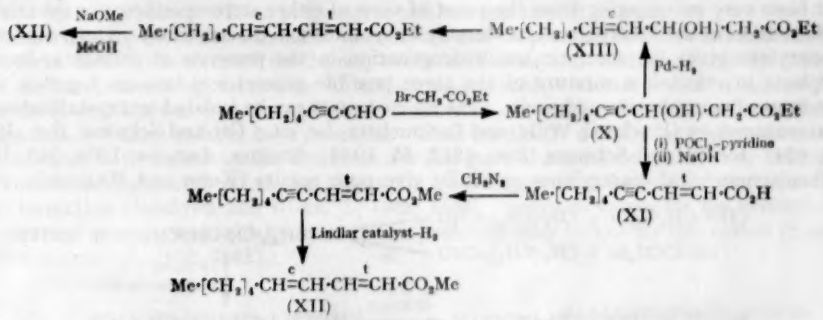
$$Me \cdot [CH_2]_4 \cdot C{\equiv}C \cdot MgX + CH(OEt)_3 \longrightarrow \underset{\text{(VIII)}}{Me \cdot [CH_2]_4 \cdot C{\equiv}C \cdot CH(OEt)_2} \xrightarrow{Pd\text{-}H_2} \underset{\text{(IX)}}{Me \cdot [CH_2]_4 \cdot \overset{c}{CH}{=}CH \cdot CH(OEt)_2}$$

$$\xrightarrow{H^+} Me \cdot [CH_2]_4 \cdot \overset{t}{CH}{=}CH \cdot CHO \xrightarrow{\text{Doebner reaction}} \textit{trans}\text{-2 : }\textit{trans}\text{-4- (V)} \qquad (c = \textit{cis};\ t = \textit{trans})$$

Deca-trans-2 : cis-*dienoic acid.* A Reformatski reaction between oct-2-ynal [derived from (VIII) above] and ethyl bromoacetate is the basis of the preparation. This is the first instance of such a reaction involving an αβ-acetylenic aldehyde (cf. Shriner, "Organic Reactions," Wiley, Vol. I, 1942, p. 1). At first the preparation was conducted in benzene with activated zinc dust, but the reaction sometimes had a long induction period and then proceeded with violence. In tetrahydrofuran, with etched zinc wool, the reaction was smooth and easily controlled. Initially, difficulty was encountered in the dehydration (X) ⟶ (XI). Treatment with potassium hydrogen sulphate or toluene-*p*-sulphonic acid gave products with ultra-violet absorption of much longer wavelength than was expected, even under conditions which effected only partial dehydration. This seems to be due to isomerisation, during the reaction, to a triene. The difficulty was overcome by use of phosphorus oxychloride–pyridine (Isler *et al.*, *Helv. Chim. Acta*, 1949, **32**, 489; Hamlet, Henbest, and Jones, *J.*, 1951, 2652) and pure enyne ester was obtained in good yield: no extraneous long-wavelength absorption was detected. Hydrolysis and crystallisations gave pure enynoic acid. Subsequent hydrogenation was carried out on methyl ester derived from this, and not on ester isolated directly from the dehydration because this last step is not necessarily stereospecific (although no evidence to the contrary was observed).

* Professor E. R. H. Jones, F.R.S., and Dr. M. C. Whiting have recently informed the author that they have now synthesised the two remaining stereoisomers (personal communication).

The pure enyne ester showed strong absorption at 961 cm.$^{-1}$, confirming the expected *trans*-2-configuration. Attempts to prepare deca-*trans*-2-en-4-ynoic acid by Doebner reaction with oct-2-ynal gave only black tars.



When methyl deca-*trans*-2-en-4-ynoate is shaken with hydrogen in presence of lead-poisoned palladium–calcium carbonate and quinoline (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446), absorption does not cease when only 1 mol. of hydrogen is absorbed. But if the process is artificially interrupted at this point, or a little earlier, methyl deca-*trans*-2 : *cis*-4-dienoate can be isolated in reasonable yield. The hydrogenation is stereospecific as far as can be judged by infra-red spectroscopy, but total selectivity (*i.e.*, hydrogenation of triple to double bond only) is not entirely achieved. Small amounts of more saturated and unchanged enyne esters need to be removed by distillation. Hydrolysis of purified ester gave the *trans*-2 : *cis*-4-acid.

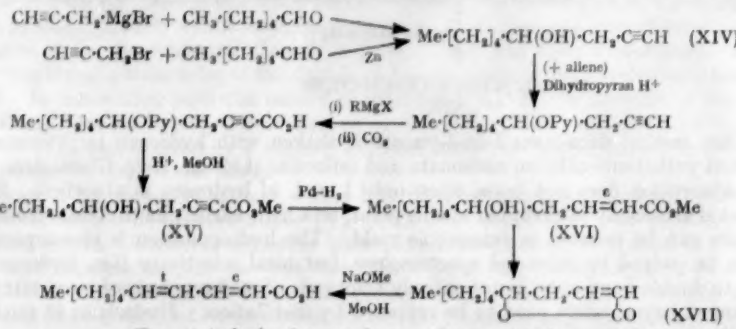
An alternative synthesis involved semihydrogenation of the hydroxy-ester (X) to the *cis*-ethylene (XIII), followed by dehydration with phosphorus oxychloride–pyridine, and ester interchange to give methyl deca-2 : 4-dienoate. Infra-red examination showed that the product was the expected *trans*-2 : *cis*-4-compound considerably contaminated with the *trans*-2 : *trans*-4-stereoisomer. This was confirmed by hydrolysis and preparation of derivatives. The *p*-bromophenacyl ester when fractionally crystallised yielded pure *trans-trans*-material as the least soluble component, whereas the *S*-benzylthiuronium salt gave, after repeated crystallisations, pure deca-*trans*-2 : *cis*-4-dienoic acid derivative. It is likely that the *trans-trans*-impurity arises by stereomutation during the dehydration stage.

Deca-cis-2 : trans-4-*dienoic acid.* Synthesis of this isomer involved non-1-yn-4-ol (XIV) which was prepared both by interaction of propargylmagnesium bromide with hexanal (Prevost, Gaudemar, and Honiberg, *Compt. rend.*, 1950, **230**, 1186; Gaudemar, *ibid.*, 1951, **233**, 64) and, better, by a Reformatski reaction between propargyl bromide and hexaldehyde (Zeile and Meyer, *Ber.*, 1942, **75**, 356; Henbest, Jones, and Walls, *J.*, 1949, 2696). 4-Hydroxynon-1-yne was converted into its tetrahydropyranyl ether, largely to increase solubility of the acetylenic Grignard reagent formed in the next step. If this was not done and the hydroxyl allowed to form a BrMg·O· derivative, poor yields ensued on carboxylation. After carboxylation, the product was heated with methanolic sulphuric acid to esterify and remove the tetrahydropyranyl residue.

Attempts to dehydrate the acetylenic hydroxy-ester (XV) by phosphorus oxychloride–pyridine were discouraging. At room temperature a chloro-derivative was obtained and on heating extensive decomposition set in. The pure ethylenic hydroxy-ester (XVI) was therefore refluxed in acid solution to give dec-2-eno-5-lactone (XVII).* On treatment with sodium methoxide in methanol for 1 hr. at 25°, according to a method used to make *cis*-2 : *trans*-4-sorbic acid (Eisner, Elvidge, and Linstead, *loc. cit.*), this lactone yielded sodium deca-*cis*-2 : *trans*-4-dienoate by stereospecific ring opening.

* This is the (±)-form of the structure proposed for massoialactone from *Cryptocarya massoia* bark oil (Meijer, *Rec. Trav. chim.*, 1940, **59**, 191) and recently confirmed by Abe and Sato (*Chem. Abs.*, 1954, 14126). Direct comparison with a natural specimen has not yet been possible.

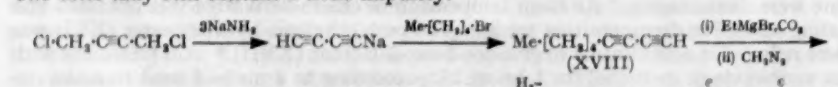
Deca-cis-2 : cis-4-dienoic acid. As there is no established method for the synthesis of *cis-cis*-stereoisomers of this type, semihydrogenation of methyl deca-2 : 4-diynoate was examined. Semireductions of diynes have been attempted before, though the results have not been very encouraging from the point of view of either stereospecificity or selectivity. Information in the literature relates largely to symmetrical diacetylenes. Thus, diphenyldiacetylene gives, on catalytic semihydrogenation in the presence of palladium–barium sulphate in ethanol, a mixture of the three possible geometrical isomers together with products of non-selective additions. The *cis-cis*-isomer can be isolated by crystallisation or chromatography (Pinckard, Wille, and Zechmeister, *loc. cit.*; Ott and Schröter, *Ber.*, 1927, **60**, 624; Kelber and Schwarz, *Ber.*, 1912, **45**, 1946; Strauss, *Annalen*, 1905, **342**, 190). Other symmetrical diacetylenes generally give poor results (Kuhn and Wallenfels, *Ber.*,



(Py = tetrahydro-2-pyranyl; c = *cis*; t = *trans*)

1938, **71**, 1889; Sargent, Thesis, London, 1948; Salkind and Gverdsiteli, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 971; *Chem. Abs.*, 1939, **33**, 8569). Riley (*J.*, 1953, 2193) recently reported that docosa-10 : 12-diynedioate gives only insignificant amounts of conjugated diene at any stage during its reaction with hydrogen in the presence of Raney nickel. On the other hand, Anet, Lythgoe, Silk, and Trippett (*J.*, 1953, 309) obtained significant increases in light absorption when oenanthotoxin (a conjugated enediynediene) absorbs 2 mols. of hydrogen in the presence of Lindlar catalyst. The products could not be isolated.

In the present case methyl deca-2 : 4-diynoate was shaken with Lindlar catalyst and quinoline in ethyl acetate. When 2 mols. of hydrogen had been absorbed (absorption showed no signs of ceasing), the reaction was interrupted and the product worked up and distilled. Examination of refractive index, ultra-violet light absorption, and microhydrogenation data of the series of fractions showed that reaction, as in the case of the enyne, was not entirely selective. Even with an allowed absorption of 1·8 mol., some ester, more saturated than diene, was isolated in the fore-runs. Nevertheless, ultra-violet light absorption shows that the major product is the diene ester, and the contaminants can be largely removed by careful distillation since acetylenic ester becomes concentrated in the later fractions and " saturated " material in the earlier. On hydrolysis, the purified ester gave a liquid acid which yielded pure crystalline derivatives, different from those of the other three acids. Spectroscopical data confirm that this is the fourth deca-2 : 4-dienoic acid (see below) and the hydrogenation is usefully stereospecific as judged from the infra-red data. The ester may still contain a little impurity.



Methyl deca-2 : 4-diynoate (XIX), needed as the intermediate, was prepared as shown from nona-1 : 3-diyne, itself synthesised according to a general method (Armitage, Jones, and Whiting, *J.*, 1951, 44). Diynes of this type can be readily carboxylated as their

Grignard complexes in the usual way (personal communication, Dr. M. C. Whiting) and deca-2 : 4-diynoic acid was obtained crystalline. After the preparation had been completed, Skattebol and Sörensen (*Acta Chem. Scand.*, 1953, **7**, 1388) reported the diyne acid and its methyl ester. Their preparative method was similar to ours.

Incidentally, opportunity was taken to compare some aspects of the infra-red and ultra-violet light absorption data of oct-2-ynal, oct-*trans*-2-enal, and octanal (Table 1). The lower carbonyl-stretching frequency of an αβ-unsaturated, compared with a saturated aldehyde is well known, but the still further decrease on conjugation with an acetylene linkage does not seem to have been recorded. Data for the 2 : 4-dinitrophenylhydrazones are consistent with values in the literature for the general classes to which they belong. The ultra-violet light absorptions for aldehydes were measured in hexane to avoid hemiacetal formation (Ashdown and Kletz, *J.*, 1948, 1454) : previous values for the extinction coefficients of αβ-acetylenic aldehydes in ethanol solution may be low for this reason (Lunt and Sondheimer, *J.*, 1950, 3361).

TABLE 1.

	Aldehyde			2 : 4-Dinitrophenylhydrazone		
	C=O (cm.$^{-1}$)	$\lambda_{max.}$ (mμ) [a]	ε	M. p.	$\lambda_{max.}$ (mμ) [b]	ε
$CH_3 \cdot [CH_2]_4 \cdot C \equiv C \cdot CHO$ [c]	1674	227	8000	80°	365	25,500
$CH_3 \cdot [CH_2]_4 \cdot CH{=}CH \cdot CHO$	1695	[d] 225, 320	[d] 9000, 27	128	374	29,000
$CH_3 \cdot [CH_2]_4 \cdot CHO$	1732	295	13	106	359	14,500

[a] In hexane. [b] In $CHCl_3$. [c] Lunt and Sondheimer (*loc. cit.*) give $\lambda_{max.}$ 227 mμ (ε 3200) for hept-2-ynal and $\lambda_{max.}$ 363 mμ (ε 25,000) for tetrolaldehyde 2 : 4-dinitrophenylhydrazone. [d] Other αβ-ethylenic aldehydes prepared in related work had $\lambda_{max.}$ 218 mμ (ε ~11,000). [e] Inflexion.

Deca-2 : 4-dienols. The four possible stereoisomers were prepared, in good yields, by lithium aluminium hydride reduction of the corresponding methyl decadienoates. Three of these were characterised as α-naphthylurethanes (Table 5).

Synthesis and Stereochemistry of Stillingic Acid.—Stillingia oil (from the seeds of *Sapium sebiferum* Roxb.) contains, as a mixed glyceride, a fatty acid with an unusually short chain (Hilditch, *J. Oil Col. Chem. Ass.*, 1949, **32**, 18; Crossley and Hilditch, *J.*, 1949, 3353). Crossley and Hilditch showed it to be an *n*-deca-2 : 4-dienoic acid as it yielded *n*-decanoic acid on hydrogenation, was oxidised to *n*-hexanoic acid by permanganate, and had its light-absorption maximum in the expected position. As they were not able to obtain satisfactory analytical data for either the liquid acid or its methyl ester and no crystalline derivatives were reported, a re-examination was undertaken.

Methyl stillingate was obtained in 3·0% yield from commercial stillingia oil. It gave excellent analytical figures for $C_{11}H_{18}O_2$ and even after storage at 0° for 12 months in a stoppered vessel the majority could be recovered pure by distillation. The acid was much less stable and gave persistently low analyses for carbon. It was characterised as the *S*-benzylthiuronium salt and *p*-bromophenacyl ester : the former was stable at 0° but the latter became resinous in a few days (after 6 hr. in air at 25° its m. p. fell by 5°). Comparison of these derivatives with those from the four stereoisomeric deca-2 : 4-dienoic acids showed that stillingic acid is deca-*trans*-2 : *cis*-4-dienoic acid (Table 2); and the infra-red

TABLE 2. *Identification of the stereochemistry of stillingic acid.*

	Me ester				*p*-Bromophenacyl ester			*S*-Benzylthiuronium salt
	B. p./mm.	n_D (20°)	$\lambda_{max.}$ (mμ)	ε	M. p.	$\lambda_{max.}$ (mμ)	ε	M. p.
Stillingic acid ...	72°/0·15	1·4884	264	22,000	71°	263	38,000	135—136°
Deca-*trans*-2 : *cis*-4-dienoic acid	75°/0·1	1·4854	265	21,000	71	263	37,500	137—138

spectra of the two methyl esters were identical. As methyl stillingate is readily available from natural sources, good supplies of a *trans*-2 : *cis*-4-dienoic acid and dienol are easily obtainable. The data in Tables 3—9 relate to naturally derived *trans*-2 : *cis*-4-compounds.

Properties of the Deca-2 : 4-dienoic Acids, Deca-2 : 4-dienols, and Their Derivatives.—The skeleton of all four methyl deca-2 : 4-dienoates was established by hydrogenation to

methyl decanoate which was identified as the *p*-bromophenacyl ester. On microhydrogenation 2 mols. of hydrogen were absorbed: light absorption data confirmed the sorbic chromophore (though the intensity fluctuations have stereochemical significance). The gross structure is thus established for each. Data on derivatives, and infra-red spectra, show without doubt that the four compounds are different homogeneous individuals. This in itself provides strong evidence that the reactions chosen in the four syntheses have led to the predicted stereoisomers. Only the *trans-trans*-isomer (as *N-iso*butylamide) forms an adduct with maleic anhydride under mild conditions, as expected from other recorded observations (for a summary see Crombie, *Quart. Reviews, loc. cit.*).

Steric stability. All of the stereoisomers show considerable resistance to stereomutation. Thus although thermal treatment (160—180° for 45 min.) led to some decomposition of the

TABLE 3. *Stereoisomeric methyl deca-2 : 4-dienoates.*

	B. p./mm.	n_D	d_4	R_D (obs.)	Exaltation [a]	Unsatn. [b]	$\lambda_{max.}$ (mμ) [c]	ε
trans-2 : *trans*-4	69—70°/0·25	1·4918 (22°)	0·9082 (22°)	58·21	4·49	2·0	260	28,500
trans-2 : *cis*-4 ...	71°/0·15	1·4874 (22°)	0·9128 (22°)	57·47	3·75	2·0	265	22,000
cis-2 : *trans*-4 ...	73°/0·35	1·4876 (23°)	0·9131 (23°)	57·47	3·75	1·9	263	23,800
cis-2 : *cis*-4 ...	74°/0·4	1·4830 (23°)	0·9095 (23°)	57·24	3·52	2·0	263	17,300

[a] Calc. mol. refractivity, 53·72 (data from Gilman, "Organic Chemistry," Wiley, 1943, Vol. II, p. 1751). [b] No. of double bonds, determined by microhydrogenation. [c] Unicam photoelectric instrument.

TABLE 4. *Derivatives of stereoisomeric deca-2 : 4-dienoic acids.*

	S-Benzylthiuronium salt.	*p*-Bromophenacyl esters					*N-iso*Butylamides				
	M. p.	M. p.	$\lambda_{max.}$ (mμ) [a]	ε	$\lambda_{max.}$ (mμ) [b]	ε	B. p./mm.	n_D (temp.)	$\lambda_{max.}$ (mμ) [c]	ε
trans-2 : *trans*-4	175°	125°	263	52,200	268	39,500	(M. p. 90°)	—	258	29,500
trans-2 : *cis*-4 ...	136	72	264	43,000	272	33,800	142°/0·1	1·5062 (20°)	258	26,000
cis-2 : *trans*-4 ...	129	82	263	39,200	270	27,500	130°/0·07	1·5088 (19°)	259	23,500
cis-2 : *cis*-4 ...	141	82	263	35,300	270	24,300	140°/0·3	1·4985 (13°)	258	17,500

[a] Unicam instrument. [b] Calc. by subtraction of the absorption curve of the *p*-bromophenacyl ester of decanoic acid [$\lambda_{max.}$ 256 mμ, ε 19,700] from that of the appropriate stereoisomer. [c] Hilger medium quartz instrument.

TABLE 5. *Stereoisomeric deca-2 : 4-dienols.*

	B. p./mm.	n_D	d_4	R_D (obs.)	Exaltation [a]	$\lambda_{max.}$ (mμ) [b]	ε	α-Naphthylurethane. M. p.
trans-2 : *trans*-4	84°/0·5	1·4857 (23°)	0·8608 (23°)	51·42	2·44	230	30,600	95°
trans-2 : *cis*-4 ...	86°/0·6	1·4870 (23°)	0·8666 (23°)	51·21	2·23	232	22,100	61
cis-2 : *trans*-4 ...	84°/0·6	1·4892 (21°)	0·8672 (21°)	51·35	2·37	232	24,000	Gum
cis-2 : *cis*-4 ...	87°/0·6	1·4852 (22°)	0·8690 (22°)	50·88	1·90	233	20,000	71

[a] Calc. mol. refractivity (Gilman, *op. cit.*), 48·98. [b] Unicam instrument.

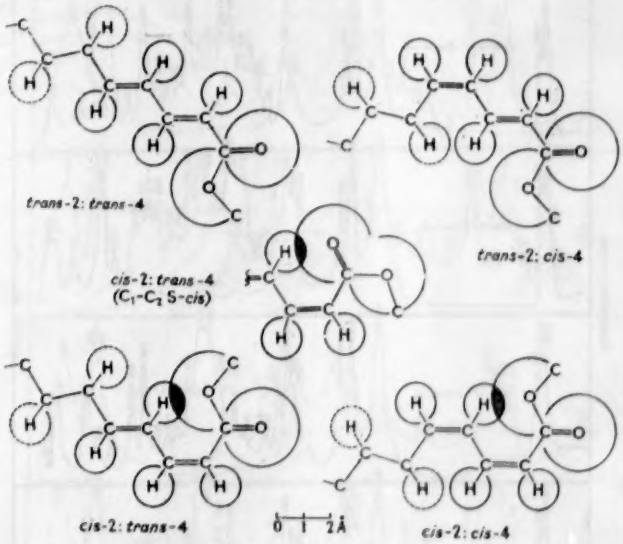
cis-2 : *cis*-4- and the *cis*-2 : *trans*-4- (and to a lesser extent the *trans*-2 : *cis*-4-)methyl ester, no stereomutation was detected by infra-red methods. Similarly, iodine-catalysed irradiation with ultra-violet light for 8 hr. caused no change. The esters were not isomerised by boiling dilute alcoholic potassium hydroxide, and no particular sensitivity to dilute mineral acid was noticed. Preparation of the four *iso*butylamides involved treatment with oxalyl chloride with liberation of hydrogen chloride, but again four different (infra-red spectra), and apparently pure, derivatives having the expected properties were obtained. Reduction of the methyl decadienoates with lithium aluminium hydride also caused no inversion (derivatives and infra-red spectra).

Physiological properties. The stereoisomeric methyl deca-2 : 4-dienoates have very similar odours though, when familiarity is gained, it is possible to distinguish between them. Similar remarks apply to the decadienols, but identification is less easy in this case. Of the

four *N-iso*butylamides, only the *trans*-2 : *trans*-4-compound has considerable sialogogue activity, but it is not as powerful as *neo*herculin or *N-iso*butyl-*trans*-2 : *trans*-4-*cis*-8 : *cis*-10-tetradecatetraenamide : the others have a bitter taste and a slight emetic effect. Only the *trans*-2 : *trans*-4- and the *trans*-2 : *cis*-4-amides have yet been tested as insecticides : both are inactive against adult *Tenebrio molitor* L., but the former is about one-third as active as the pyrethrins against adult *Musca domestica*. The *trans*-2 : *cis*-4- is less than one-tenth as active as the *trans*-2 : *trans*-4-amide and the latter is two-fifths as active as the fraction A and B mentioned in Part IV. In the author's experience so far, sialogogue effect is always associated with insecticidal activity in this group of amides.

Physical properties. The four methyl esters and the alcohols are liquid : all the acids and *iso*butylamides are liquid except the *trans-trans*-isomers. Similarly, when the

FIG. 1. *Planar projection diagrams of the chromophores of stereoisomeric methyl deca*-2 : 4-*dienoates.*



The following values are used for bond lengths : C=C 1·34 ; *s*-C–C 1·44 ; C–C 1·54 ; C–H 1·09 ; C=O 1·20 Å (cf. Lonsdale, Robertson, and Woodward, *Proc. Roy. Soc.*, 1941, *A*, **178**, 43). Bond angles : C–C=C 123° ; C–C=O 120°. The van der Waals radius for oxygen is taken as 1·40 and for hydrogen 0·75 Å.

derivatives are crystalline, the *trans-trans*-compound has the highest m. p. This is to be associated with linear character which allows tight packing in the crystal lattice (see Parts I and II). The stereoisomer with the next highest m. p. is usually the *cis-cis*-compound and examination of models suggests that this is because the *cis-cis*- is more nearly linear than the *trans-cis*-chain.

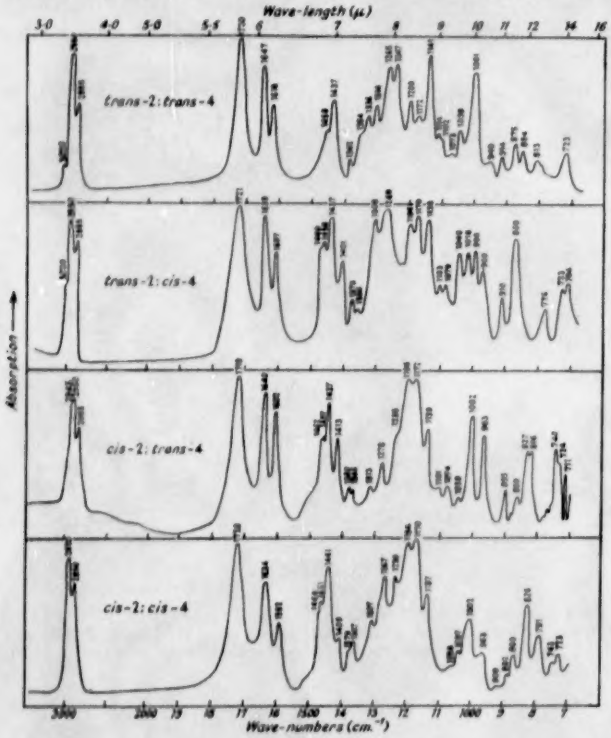
Exaltations of molecular refractivities of the methyl decadienoates decrease in the order *trans*-2 : *trans*-4 > *cis*-2 : *trans*-4 ≈ *trans*-2 : *cis*-4 > *cis*-2 : *cis*-4. In the decadienols the sequence is similar. If exaltation is taken as a measure of conjugation then it too follows the above order.

Ultra-violet light absorption data. These are recorded for the deca-2 : 4-dienoic acids, their methyl esters, *p*-bromophenacyl esters, and *iso*butylamides, and the deca-2 : 4-dienols (Tables 3 and 4). The stereochemistry of the diene system has only slight influence on the position of maximal absorption. Nevertheless, it is perhaps just significant that for the *trans-trans*-dienols and methyl esters, $\lambda_{max.}$ lies at a measurably lower position than for the other stereoisomers (cf. Celmer and Solomons, *J. Amer. Chem. Soc.*, 1953, **75**, 3430;

Nichols, Herb, and Riemenschneider, *ibid.*, 1951, **73**, 247). The alteration indicates a small change in electronic transition energy: this is noticeable in passing from a *trans-trans-trans-* ($\lambda_{max.}$ 268 mμ) to a *trans-trans-cis*-triene ($\lambda_{max.}$ 271 mμ; see Crombie and Tayler, *J.*, 1954, 2816).

The extinction coefficients of the methyl deca-2 : 4-dienoates decrease in the same order as molecular exaltation and, presumably, the conjugation. The change from methyl deca-*trans*-2 : *trans*-4- to -*trans*-2 : *cis*-4-dienoate will first be examined. The lower ε of the *trans*-2 : *cis*-4-isomer is unlikely to be associated with contamination caused by over-hydrogenation as the values for the synthetic and the natural specimen agree well (Table 2).

FIG. 2. *Infra-red spectra of methyl deca-2 : 4-dienoates (pure liquid films).*

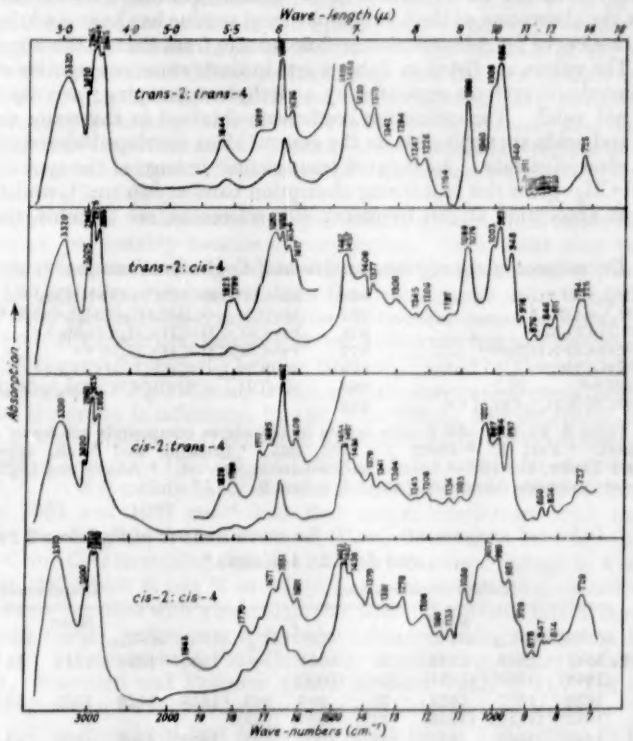


The chromophore length ($C_{(5)}$ to the centre of the O of the C=O) is the same (6·0 Å) in each case, if the reasonable assumption is made that linkages joining the double bonds are in the *s-trans*-configuration (Fig. 1). Static models can be constructed (even using Courtauld atomic models: these over-accentuate steric hindrance for many spectroscopic purposes), which allow complete planarity of the chromophore without any considerable hindrance effects. However, the *trans*-2 : *cis*-4 model makes it clear that there must be repulsion between the two *cis*-substituents and that rotation of the *n*-pentyl residue will meet with considerable hindrance from the hydrogen atom on $C_{(3)}$. The two effects are related. Neither operates for the *trans*-2 : *trans*-4-compound and this may explain spectroscopical differences as follows.

Possible consequences of the repulsion are opening of the bond angles with retention of coplanarity of the four substituents attached to the *cis*-double bond, or movement of one substituent to above and of another to below the formal plane of the carbon–carbon double

bond. The latter state of affairs can be regarded as due to rotation of the double bond through a small angle (the energy required for this limited rotation is likely to be small, though quantitative data are difficult to obtain; see Mulliken and Roothaan, *Chem. Reviews*, 1947, **41**, 219). As a consequence, there is a decrease in overlap of the two p-electrons in the π-orbital and this is reflected in the infra-red spectrum (see below). The departure from planarity and opening of bond angles will also help to lower the energy barrier to free rotation of the alkyl group. It can be still further reduced by rotation on the $C_{(3)}$–$C_{(4)}$ s-bond, which decreases resonance energy and partly destroys coplanarity of the chromophore. The effect is again to decrease $\varepsilon_{max.}$ (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Braude, Sondheimer, and Forbes, *Nature*, 1954,

FIG. 3. *Infra-red spectra of deca-2 : 4-dienols (pure liquid films; upper curve, ~150 micron film).*



173, 117; see also Brooker, White, Sprague, Dent, and Van Zandt, *Chem. Reviews*, 1947, **41**, 325; Ferguson, *ibid.*, 1948, **43**, 385).

The case of the *cis*-2 : *trans*-4-stereoisomer is more complicated. The chromophore length defined as above is shorter (5·45 Å) on the assumption of an all *s-trans*-structure (Fig. 1). Furthermore, an *s-cis*-bond for the $C_{(1)}$–$C_{(2)}$ linkage is acceptable as it results in somewhat reduced interaction with the $C_{(4)}$-hydrogen atom (chromophore length 3·85 Å). This chromophore-length effect could be the cause of a reduced extinction coefficient, as the latter depends on dipole moment and is proportional to the square of the distance between the ends of the conjugated system (Zechmeister, Le Rosen, Schroeder, Polgar, and Pauling, *J. Amer. Chem. Soc.*, 1943, **65**, 1940). Apart from this, there is steric hindrance between the $C_{(4)}$-hydrogen and an oxygen atom in both conformations. Finally, in the *s-trans*-form, the $C_{(4)}$-hydrogen atom presents a barrier to rotation of the methoxyl of the methoxycarbonyl grouping which could be relieved only by rotation of single or double carbon–

carbon linkages as discussed above. Chromophore lengths in the two possible conformations of the *cis-cis*-isomer ($C_{(1)}$–$C_{(2)}$ *s-trans* or *s-cis*) are the same as for the *cis*-2 : *trans*-4-compound and the same remarks apply. In addition there are the effects caused by the *cis*-$C_{(4)}$–$C_{(5)}$ double bond and referred to in the discussion of the *trans*-2-*cis*-4-compound. It is not surprising that the extinction coefficient is lowered still more.

The four deca-2 : 4-dienols are of interest as the diene chromophore length is formally the same in all four cases, if $C_{(3)}$–$C_{(4)}$ is assumed to be *s-trans* (there is, however, probably some hyperconjugation involving the oxygen). On a static model there is no severe inhibition of coplanarity. But again there is the characteristic sequence of decreasing $\epsilon_{max.}$ found in the methyl esters, which can be explained by applying repulsion and hindrance to rotation in *cis*-forms, as outlined above. The *trans-trans*-isomer is completely free from such effects, which are greatest in the *cis-cis*-form. In the *p*-bromophenacyl esters, an approximate correction for the absorption of the *p*-bromophenacyl residue has been made by subtraction of the extinction curve for *p*-bromophenacyl decanoate from that of the appropriate diene derivative. The values are listed in Table 4 and indicate some conjugative effect between the two chromophoric systems separated by a methylene grouping; strictly speaking, the procedure is not valid. The extinction coefficients obtained in this series and in the *iso*-butylamides and acids are explicable on the general ideas developed above.

Infra-red absorption data. An isolated *trans*-olefinic linkage of the type $-CH_2{\cdot}CH{=}CH{\cdot}CH_2-$ gives rise to a strong absorption band at 966 cm.$^{-1}$, whilst a *cis*-linkage has little or no absorption at this frequency (for references, see Crombie, *Quart. Reviews*, *loc. cit.*). The cause of the absorption is believed to be an out-of-plane deformation vibration of the two hydrogen atoms attached *trans* to the double bond. Conjugative influences with carboxyl, phenyl, or other double bonds cause a shift to higher frequencies (Table 6). In contrast, conjugation with an acetylenic linkage causes a shift to lower frequencies. The positions of the absorption seem little influenced by the physical state of the specimen (mull, liquid film, or solution). Whilst the present work was in progress, Jackson, Paschke, Boyd, Tolberg, and Wheeler (*J. Amer. Oil Chem. Soc.*, 1952, 229)

TABLE 6. *Dependence of out-of-plane unsaturated* C–H *vibrations* (*cm.*$^{-1}$) *on conjugation.*

$Pr^n{\cdot}CH{=}CH{\cdot}[CH_2]_3{\cdot}OH$ [a]	968	$Me{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i$ [b]	990
$Me{\cdot}CH{=}CH{\cdot}[CH_2]_3{\cdot}COMe$ [a]	967	$Me{\cdot}[CH_2]_2{\cdot}[CH{=}CH]_2{\cdot}[CH_2]_7{\cdot}CO_2H$ [b,f]	998
$Me{\cdot}[CH_2]_4{\cdot}CH{=}CH{\cdot}CO_2Me$ [a]	978	$Pr^n{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CO_2Me$ [a,g]	950
$Me{\cdot}[CH_2]_4{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i$ [b,c]	977	$Pr^n{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2Br$ [a,g]	950
$Me{\cdot}[CH_2]_4{\cdot}CH{=}CH{\cdot}CHO$ [a]	978	$Me{\cdot}[CH_2]_4{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2Et$ [a]	961
$Ph{\cdot}CH{=}CH{\cdot}CO_2H$ [b,d]	980	$Me{\cdot}[CH_2]_4{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}[CH_2]_7{\cdot}CO_2Me$ [a,h]	955
$Me{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}[CH_2]_3{\cdot}CO_2H$ [b,e]	988		

See also Table 3, Part I. All double bonds in the above compounds are *trans*. [a] Liquid film. [b] Paraffin mull. [c] Part I. [d] Flett, *J.*, 1951, 963. [e] Crombie and Shah, unpublished work. [f] Crombie and Tayler, *loc. cit.* [g] Celmer and Solomons, *loc. cit.* [h] Ahlers and Ligthelm, *J.*, 1952, 5039. For stereoisomeric dienes see Tables 7, 8, and 9.

TABLE 7. *Infra-red assignments* (*cm.*$^{-1}$) *for stereoisomeric methyl deca-2 : 4-dienoates and deca-2 : 4-dienols.*[a]

	Methyl decadienoates						Decadienols					
			Mean		δ′				Mean		δ′	
	νC=C$_I$	νC=C$_{II}$	νC=C	ΔC=C	[CH=CH]$_2$		νC=C$_I$	νC=C$_{II}$	νC=C	ΔC=C	[CH=CH]$_2$	
trans-2 : *trans*-4	1647	1618	1633	29	1001	—	1660	1626	1643	34	986	—
	(1648)	(1620)	(1634)	(28)	(1000)	—						
trans-2 : *cis*-4 ...	1639	1607	1623	32	996	969	1655	1616	1635	39	983	948
	(1642)	(1610)	(1626)	(32)	(995)	(969)						
cis-2 : *trans*-4 ...	1640	1602	1621	38	1002	963	1652	1609	1630	43	984	952
	(1642)	(1603)	(1622)	(39)	(1001)	(963)						
cis-2 : *cis*-4 ...	1634	1592	1613	42	1002[b]	963[b]	1651	1601	1626	50	985[b]	951[b]
	(1637)	(1594)	(1616)	(43)	(1002)[b]	(963)[b]						

[a] All liquid films, but figures in parentheses represent measurements on a 10% solution in CCl_4. The suffixes I and II denote the bands of higher and lower frequency respectively. [b] Relevance uncertain: may be due to impurity.

suggested that in *cis-trans*-dienes a band at 942 cm.$^{-1}$, as well as one at 982 cm.$^{-1}$, was characteristic of the configuration. Some support for this is found in the report by Celmer and Solomons (*loc. cit.*); they find that nona-*trans*-3 : *cis*-5-dienoic acid and trideca-*trans*-3 : *cis*-5-dienoic acid have bands at 1020, 985, and 950 cm.$^{-1}$.

The position of the stretching frequency of a C=C (unconjugated with other olefinic linkages) and geometrical configuration were correlated in Part I. *cis*-Isomers absorb at some 10—15 cm.$^{-1}$ lower than the *trans*-forms. A similar effect is found in the Raman spectra of monoethenoid geometrical isomers (see references cited in Part I) and its implications regarding the spectra of dienes are examined below. The infra-red data obtained in this investigation are discussed broadly under three headings: (i) the olefinic C–H deformation region; (ii) the C=C and C=O stretching region; and (iii) other regions.

(i) The olefinic C–H out-of-plane deformation region. Table 7 shows that in the deca-2 : 4-dienols the *trans-trans*-isomer has a band only at 986 cm.$^{-1}$ whilst the two *cis-trans*-compounds have a second band at 950 cm.$^{-1}$. The position of the second band agrees better with the results of Celmer and Solomons than those of Jackson *et al.*, possibly because the diene system, in the two cases cited by the latter authors, was seated deeply in a long chain, remote from polar influences. The *cis-cis*-stereoisomer also has absorption at 984 and 950 cm.$^{-1}$ but because of difficulties in purification further information is required before these are accepted as characteristic: *cis-trans* impurity could be responsible, as also for the *cis-cis* methyl ester.

In the methyl deca-2 : 4-dienoates and the *iso*butylamides both bands are shifted to higher frequencies, presumably because of conjugation. Such shifts must be taken into account for determinations of configuration. Intensity measurements in this region may be valuable; in particular, the two bands in the *cis-cis*-isomer are weak but it has not yet been possible to undertake quantitative extinction measurements. A band at 1016 cm.$^{-1}$ is present for methyl deca-*trans*-2 : *cis*-4-dienoate but not for the other stereoisomers and may correspond with the band at 1020 cm.$^{-1}$ noted by Celmer and Solomons.

For the decadienols, a CH_2·OH group would normally have a C–O stretching vibration at 1060 cm.$^{-1}$ but the group is influenced by electronic effects, and unsaturation causes the band to move to lower frequencies because of the decreased C–O force constant (Zeiss and Tsutsui, *J. Amer. Chem. Soc.*, 1953, **75**, 897), though in no case so far observed does it fall below 1000 cm.$^{-1}$. It is therefore likely that the assignment can be made to the strong band lying between 1003 and 1027 cm.$^{-1}$ and that major interference with the 986-cm.$^{-1}$ vibration is not experienced.

(ii) The C=C and C=O stretching region. An isolated olefinic linkage in a compound of the type CHR=CHR′ where R and R′ are alkyl, has a weak stretching vibration at 1660—1670 cm.$^{-1}$. On conjugation with a second double bond, vibrational interaction occurs and two weak bands appear, unless one is forbidden by molecular symmetry, at ~1635—1650 and 1600 cm.$^{-1}$ (Rasmussen, " Fortschritte der Chemie Organischer Naturstoffe, 1948, Vol. V, p. 331; Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1). The influence of geometrical configuration on these vibrations has not hitherto been studied. The methyl decadienoates will be considered first as the two diene bands ($C{=}C_I$ refers to the band of higher and $C{=}C_{II}$ to that of lower frequency) are strong and easily recognisable because of the proximity of the groups to the methoxycarbonyl group. There is a movement of both bands (particularly $C{=}C_{II}$) to lower frequencies as one passes from the *trans-trans*- through the two *cis-trans*- to the *cis-cis*-isomer. At the same time, the separation constant Δ increases also. The position of the carbonyl stretching vibration is constant within experimental error and all the bands are hardly affected on remeasurement in 5 or 10% solution in carbon tetrachloride. Similar results are obtained for the *p*-bromophenacyl esters, though the $C{=}C_{II}$ vibration seems to lie, as would be expected, under the $phenyl_I$ vibration in the case of the *cis-cis*-compound. This characteristic behaviour of the double-bond vibrations should prove useful for recognition of the geometrical configurations of dienes.

The *N-iso*butyldeca-2 : 4-dienamides present a more complex problem. Here, the amide A (C=O type) lies close to the $C{=}C_I$ and the $C{=}C_{II}$ vibration, and the arguments for the assignments presented in Table 9 are as follows. *N-iso*Butyldecanamide has its amide A vibration, unequivocally, at 1642 cm.$^{-1}$. *N-iso*Butyldeca-*trans*-2-enamide has two strong

vibrations at 1629 and 1671 cm.$^{-1}$. On conjugation, the amide A carbonyl vibration must fall to lower frequencies, so the band at 1629 cm.$^{-1}$ is assigned to this. In conformity *N-iso*butyldec-*cis*-2-enamide has strong bands at 1631 and 1660 cm.$^{-1}$, *i.e.*, the shift due to *cis*-configuration (mentioned above and known from other examples in the infra-red and Raman spectra: see Parts I and II) has occurred on the other band (C=C), as expected. We thus also expect the amide A vibration to fall a little further by conjugation with a

TABLE 8. *Infra-red assignments (cm.$^{-1}$) for stereoisomeric* p-*bromophenacyl deca-2 : 4-dienoates.*[a,b]

	Ester νC=O	Keto νC=O	νC=C$_I$[c]	νC=C$_{II}$[c]	Mean νC=C	ΔC=C	Ph$_I$[c]	Ph$_{II}$[c]
trans-2 : *trans*-4	1719	1702	1640	1617	1628	23	1586	1483
trans-2 : *cis*-4	1711	1694	1631	1602	1617	29	1588	1486
cis-2 : *trans*-4	1714	1696	1640	1600	1620	40	1588	1486
cis-2 : *cis*-4	1714	1694	1636	—[d]	—	—	1587	1485

[a] *p*-Bromophenacyl decanoate had ester C=O 1741, keto C=O 1701, Ph$_I$ 1588, Ph$_{II}$ 1485 cm.$^{-1}$. [b] Paraffin mulls. [c] For the meaning of the suffixes see note to Table 7. [d] Obscured by Ph$_I$ vibration.

TABLE 9. *Infra-red assignments (cm.$^{-1}$) for stereoisomeric* N-iso*butyldeca-2 : 4-dienamides.*

	νNH		Amide A νC=O	νC=C$_I$[f]	νC=C$_{II}$[f]	Mean νC=C	ΔC=C	Amide B νC=O	δ′ [CH=CH]$_2$	
trans-2 : *trans*-4[a]	3295	3075	1625[e]	1654[e]	1614[e]	1634	40	1550	994[e]	—
trans-2 : *cis*-4[b] ...	3285	3075	1623	1653	1609[d]	1631	44	1549	993	963
cis-2 : *trans*-4[b] ...	3285	3090	1632[e]	1650[e]	1605[e]	1627	45	1544	998[e]	961[e]
cis-2 : *cis*-4[b]	3285	3075	1628	1649	1595[d]	1622	54	1546	994	962

[a] Paraffin mull. [b] Liquid film. [c] *trans*-2 : *trans*-4-Sorbic *iso*butylamide (paraffin mull) had the corresponding bands at 1629, 1655, 1618, and 990 cm.$^{-1}$. [d] Incompletely resolved. [e] *cis*-2 : *trans*-4-Sorbic *iso*butylamide (paraffin mull) had the corresponding bands at 1634, 1652, 1605, 991, and 961 cm.$^{-1}$ [prepared by Miss U. Eisner (Eisner, Elvidge, and Linstead, *loc. cit.*]. [f] See note to Table 7.

second double bond (comparison of methyl dec-*trans*-2-enoate with methyl deca-*trans*-2 : *trans*-4-dienoate indicates about 6 cm.$^{-1}$). In *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide the band at 1625 cm.$^{-1}$ is therefore identified as amide A vibration, and the two bands at 1654 and 1614 cm.$^{-1}$ are assigned to the C=C$_I$ and the C=C$_{II}$ vibration respectively.

The values for the double bond vibrations (Table 9) in the four stereoisomers then show regular shifts similar to those just mentioned. Further, the amide A vibration has slightly higher values in the two compounds with *cis*-2 double bonds. Models indicate that this may be due to a steric effect, the C$_{(4)}$-hydrogen atom forcing the carbonyl of the bulky amide group sufficiently out of planarity to have slight effects on the frequency.

The C=C$_I$ and C=C$_{II}$ vibrations of the four deca-2 : 4-dienols are weak compared with those discussed above but, if thick films are used, they are readily recognised, though unidentified bands, probably overtones and combination tones, intrude. Because there is no conjugation with a carboxylic function, all the frequencies are higher. The characteristic general fall of frequencies and increase in Δ values on passing from *trans-trans-* to *cis-cis*-amide agrees with the other cases.

(iii) Other regions. A few other features may be useful for stereochemical identification in related cases. In the deca-2 : 4-dienoic esters a band at 1401—1413 cm.$^{-1}$ is absent only from the *trans*-2 : *trans*-4-form though it lies at shorter wave-lengths in the *trans*-2 : *cis*-4-isomer. All the esters have moderately strong bands at 1137—1141 cm.$^{-1}$ (possibly an ester C–O vibration); the very weak character, relative to it, of the band at 1172 cm.$^{-1}$ is worthy of note for the *trans*-2 : *trans*-4-compound. Only the *cis*-2 : *trans*-4-decadienol has no strong vibration near 1089 cm.$^{-1}$. The O–H stretching band lies at 3310—3330 cm.$^{-1}$, and the band between 720 and 730 cm.$^{-1}$ is probably an alkyl-chain bending vibration.

Results (Tables 7, 8, and 9) for the C=C$_I$ and C=C$_{II}$ stretching frequencies require further comment. If hindrance, reflected in the ultra-violet spectra for systems containing *cis*-linkages, caused only an adjustment of the diene system from coplanarity by rotation

on *s*-bonds, then, so far as the C=C stretching vibrations are concerned one would expect the effects of conjugation to be decreased, *i.e.*, they would move to higher frequencies on passing through the series *trans-trans*, *cis-trans*, and *trans-cis*, to *cis-cis*. In fact they move to lower frequencies. This can be explained if hindrance is relieved, or repulsion reduced, by angular twisting of the carbon–carbon double bond, with decrease in its force constant and a marked shift to lower frequencies : this effect might well overpower an opposing shift due to the *s*-bond adjustment. Such an explanation agrees with the fact mentioned above that the more hindered *cis*-mono-olefins absorb at lower frequencies than the *trans*-forms, in both infra-red and Raman spectra.

In the light of the synthetical work reported here, it is believed that essentially stereospecific synthesis of compounds of the type R·CH=CH·CH=CH·R′ containing any of the four stereochemical possibilities is feasible, and in this respect synthetical methods are ahead of diagnostic ones.

Experimental

For general remarks see preceding paper. For many physical data see Tables.

1 : 1-*Diethoxyoct-2-yne*.—Methylmagnesium bromide was prepared in ether (700 ml.) from magnesium (24 g.). Hept-1-yne (96 g.) was added slowly and the mixture then refluxed for 6 hr. Ethyl orthoformate (163 g., 1·1 mol.) was added to the cooled acetylenic Grignard reagent and refluxing continued for 6 hr. more. Ice and water were added, the ether layer was removed, and the aqueous phase treated with acetic acid (100 ml.) and extracted twice with ether. The ethereal solutions were united, washed with sodium hydrogen carbonate, and dried (Na_2SO_4). Evaporation and distillation yielded 1 : 1-diethoxyoct-2-yne (150 g., 77%), b. p. 120—123°/18 mm., n_D^{15} 1·4382 (Moureu and Delange, *Bull. Soc. chim.*, 1904, **31**, 1333, give b. p. 118—125°/20 mm., n_D^{19} 1·438).

cis-1 : 1-*Diethoxyoct-2-ene*.—1 : 1-Diethoxyoct-2-yne (26·0 g.) was hydrogenated in ethyl acetate (10 ml.) with palladium–calcium carbonate (5%; 1·0 g.) until 3·10 l. of gas had been absorbed at 16°/740 mm. (required for semihydrogenation, 2·94 l.). Kieselguhr was added and the catalyst removed by filtration. Evaporation and distillation gave cis-1 : 1-*diethoxyoct-2-ene* (18·3 g., 70%), b. p. 116—118°/30 mm., n_D^{21} 1·4292 (Found : C, 71·7; H, 11·8. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·05%).

trans-*Oct-2-enal*.—1 : 1-Diethoxyoct-2-ene (14·5 g.) was refluxed with 5% sulphuric acid (100 ml.) for 3 hr. The brown upper layer was removed with ether, dried, and distilled, giving *trans*-oct-2-enal (7·3 g., 80%), b. p. 84—86°/19 mm., n_D^{24} 1·4485 (Found : C, 76·1; H, 11·25. $C_8H_{14}O$ requires C, 76·15; H, 11·2%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as orange needles, m. p. 128° (Found : C, 54·8; H, 5·85. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9%). Van Romburgh (*Rec. trav. chim.*, 1938, **57**, 494) records that an oct-2-enal (b. p. 83°/14 mm.) occurs in the essential oil of *Achasma walang* Val.

***Deca*-trans-2 : trans-4-*dienoic Acid*.**—Pyridine (12 ml.) and *trans*-octenal (16·8 g.) were mixed, and malonic acid (13·8 g.) was added slowly, with shaking. After 2 days at 20°, all the solid material had dissolved and the orange yellow liquid was heated to 100° for 30 min., then cooled and poured into ice-cold, dilute sulphuric acid. The crude product was extracted with ether, and the acid extracted from this with 10% aqueous sodium hydroxide. *Deca*-trans-2 : trans-4-*dienoic acid* was liberated at 0° with dilute sulphuric acid, collected with ether, and purified by distillation (8·15 g., 37%), having b. p. 121—124°/0·3 mm., n_D^{21} 1·5058. It rapidly crystallised in plates. Recrystallisation from light petroleum gave the acid, m. p. 49—50° (Found : C, 71·55; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Light absorption : max. at 257 mμ (ε 28,500) (by the photographic method, a subsidiary maximum or inflexion can be observed at 264 mμ in many of the measurements on the dienoic acids and their derivatives : it is not observed by the photoelectric method; cf. Parts IV and V). The *p-bromophenacyl ester* crystallised as needles from ethanol (Found : C, 59·0; H, 5·85. $C_{18}H_{21}O_3Br$ requires C, 59·2; H, 5·8%). The *S-benzylthiuronium salt* was readily formed (Found : C, 64·8; H, 7·8. $C_{18}H_{26}O_2N_2S$ requires C, 64·65; H, 7·85%). As in the case of the *S*-benzylthiuronium salts mentioned below, the m. p. is somewhat dependent on the rate of heating (cf. Berger, *Acta Chem. Scand.*, 1954, **8**, 427). *Methyl deca*-trans-2 : trans-4-*dienoate*, prepared by use of diazomethane (0·61 g. of acid gave 0·43 g. of ester), had b. p. 69—70°/0·25 mm., n_D^{20} 1·4928, or, prepared by use of methanol containing a trace of sulphuric acid (0·97 g. of acid gave 0·85 g. of ester), had b. p. 87—89°/13 mm., n_D^{17} 1·4937 (Found : C, 72·45; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%).

n-*Oct-2-ynal*.—1 : 1-Diethoxyoct-2-yne (31·2 g.) was refluxed with 4% sulphuric acid (100 ml.) for 4 hr., cooled, and extracted with ether. Evaporation and distillation of the brown extract gave oct-2-ynal (14·2 g., 73%), b. p. 74—76°/15 mm., 86—88°/27 mm., n_D^{20} 1·4499 (Found: C, 77·4; H, 9·85. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·75%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange laths, m. p. 80° (Found: C, 55·2; H, 5·4; N, 17·9. $C_{14}H_{16}O_4N_4$ requires C, 55·25; H, 5·3; N, 18·4%).

Ethyl 3-*Hydroxydec*-4-*ynoate*.—Activated zinc dust (4·0 g.) was covered with benzene (80 ml.), and ethyl bromoacetate (9·0 g.) mixed with oct-2-ynal (6·2 g.) was added in portions, with refluxing, until reaction commenced. When all of the reagents had been added, the mixture was heated on the steam-bath for 90 min. The benzene layer was decanted and unchanged zinc washed with benzene. These benzene solutions were united and washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate, and then dried. Removal of solvent and two distillations yielded *ethyl* 3-*hydroxydec*-4-*ynoate* (5·0 g., 47%), b. p. 103—104°/0·2 mm., $n_D^{20\cdot5}$ 1·4556 (Found: C, 68·35; H, 9·55. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·5%). Microhydrogenation required 2·52H_2 (triple bond and partial hydrogenolysis of the hydroxyl grouping). Light absorption: none having $E_{1\,cm.}^{1\%}$ >30 observed. Infra-red absorption: strong wide band at 3450 cm.$^{-1}$ (hydroxyl) and medium-weak band at 2224 cm.$^{-1}$ (C≡C).

Methyl 3-*Hydroxydec*-4-*ynoate*.—Zinc wool (6·0 g.) was activated by treatment with dilute acid, washed, dried, and covered with tetrahydrofuran (10 ml.). A little mercuric chloride was added and the mixture heated to the b. p. Oct-2-ynal (10 g.) and methyl bromoacetate (14 g.) were mixed in tetrahydrofuran, and a small amount was added to the zinc. A smooth reaction soon began. The mixture was removed from the bath, and the remaining reactants were added at such a rate as to maintain gentle refluxing. After 1 hour's heating the product was cooled and poured into ice and acetic acid. This mixture was saturated with sodium chloride and extracted with ether (4 times). The extracts were washed with aqueous sodium hydrogen carbonate, dried, and distilled, to give methyl 3-hydroxydec-4-ynoate (8·2 g., 52%), b. p. 94—100°/0·4 mm., n_D^{18} 1·4665. Dehydration by phosphorus oxychloride–pyridine (see below) gave methyl dec-2-en-4-ynoate, b. p. 86—92°/0·5 mm., n_D^{20} 1·4868.

Ethyl Dec-2-*en*-4-*ynoate*.—Ethyl 3-hydroxydec-4-ynoate (2·1 g.) was mixed with pyridine (3·0 ml.), and phosphorus oxychloride (3·5 ml.) in pyridine (10 ml.) was added with ice-cooling. The product was heated to 100° for 3½ hr.; it darkened considerably. It was poured into ice-water and extracted with ether. The extract was washed with dilute hydrochloric acid and sodium hydrogen carbonate solution, dried, and distilled, to give *ethyl dec*-2-*en*-4-*ynoate* (1·30 g.), b. p. 85—87°/0·2 mm., n_D^{23} 1·4819 (Found: C, 74·2; H, 9·3. $C_{12}H_{18}O_2$ requires C, 74·15; H, 9·35%). Microhydrogenation required 2·85H_2. Light absorption: max. at 251, 258, 264 mμ ($E_{1\,cm.}^{1\%}$ 780, 870, 870; ε 15,200, 16,800, 16,800). The vibrational spectrum showed bands (*inter alia*) at 2212 (C≡C), 1720 (C=O), and 1619 (C=C) cm.$^{-1}$. Methyl dec-*trans*-2-enoate has bands at 1726 (C=O) and 1655 (C=C) whilst methyl decanoate has one strong band at 1744(C=O) cm.$^{-1}$ (all liquid films.).

Dehydration with potassium hydrogen sulphate or toluene-*p*-sulphonic acid gave mixtures.

Ethyl 3-*Hydroxydec*-cis-4-*enoate*.—Ethyl 3-hydroxydec-4-ynoate (4·6 g.) was hydrogenated in ethyl acetate (5 ml.) with 5% palladium–calcium carbonate. When 510 ml. of hydrogen had been absorbed (511 ml. at 19°/772 mm. for semi-hydrogenation), kieselguhr was added and the catalyst filtered off. Evaporation and distillation yielded *ethyl* 3-*hydroxydec*-cis-2-*enoate* (3·3 g.), b. p. 98—100°/0·4 mm., n_D^{20} 1·4504 (Found: C, 67·7; H, 10·4. $C_{12}H_{22}O_3$ requires C, 67·25; H, 10·35%). Light absorption: no maximum of $E_{1\,cm.}^{1\%}$ >10.

Dehydration of Ethyl 3-*Hydroxydec*-cis-4-*enoate*.—The *cis*-hydroxy-ester (1·86 g.) was diluted with pyridine (2·5 ml.), and phosphorus oxychloride (3·0 g.) in pyridine (9 ml.) was added. The mixture was heated on a steam-bath for 3½ hr., poured into water, and worked up as described for ethyl dec-2-en-4-ynoate. The *diene ester* (1·05 g.) had b. p. 90—91°/0·5 mm., n_D^{18} 1·4818 (Found: C, 72·8; H, 10·25. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·25%). Microhydrogenation 1·97H_2. Light absorption: max. at 264 mμ (ε 22,100). This ester was converted, by setting it aside in methanol containing a little sodium methoxide for 16 hr., into the *methyl ester*, b. p. 67—68°/0·13 mm., n_D^{25} 1·4855 (Found: C, 72·15; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·6; H, 9·9%). Microhydrogenation required 1·89H_2. Light absorption: max. at 265 mμ (ε 22,900).

Use of potassium hydrogen sulphate gave a mixture.

Hydrolysis of this ester (1·19 g.), as described below for methyl stillingate, yielded a deca-2 : 4-dienoic acid (0·93 g.), b. p. 130°/0·6 mm., n_D^{26} 1·5020 (Found: C, 70·45; H, 9·75%). Microhydrogenation required 1·87H_2. Light absorption: max. at 258 mμ (ε 20,200). The *p*-bromophenacyl ester initially melted unsharply at ~110° and after three recrystallisations

from ethanol formed flat shining crystals, m. p. 121—122° which, when admixed with an authentic specimen of the *trans-trans*-ester (m. p. 124·5°), had m. p. 122—124°. The acid gave an *S*-benzylthiuronium salt, m. p. 132—137° (crude). When crystallised from ethyl acetate, a derivative of m. p. 134° was obtained, undepressed on admixture with the authentic *trans*-2 : *cis*-4-derivative.

Dec-trans-2-*en*-4-*ynoic Acid*.—The ethyl ester (2·6 g.) was hydrolysed with potassium hydroxide (1·0 g.) in methanol (5 ml.). Working up in the usual way gave the crude acid (2·15 g., 97%) which solidified. Crystallisation from light petroleum gave pure *dec*-trans-2-*en*-4-*ynoic acid*, m. p. 46—47°, as needles (Found: C, 71·95; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%). Microhydrogenation required 2·85H_2. Light absorption: max. at 257 mμ (ε 15,800). The p-*bromophenacyl ester* crystallised in plates (from ethanol), m. p. 114° (Found: C, 59·5; H, 5·5. $C_{18}H_{19}OBr$ requires C, 59·5; H, 5·3%). Light absorption: max. at 264 mμ (ε 36,300). The *methyl ester* was prepared by esterification with diazomethane and had n_D^{28} 1·4852 (Found: C, 72·7; H, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%).

Methyl Deca-trans-2 : cis-4-*dienoate*.—The above enyne ester (0·959 g.) was dissolved in methanol (5 ml.), and lead-poisoned palladium catalyst, prepared according to Lindlar (*loc. cit.*), was added together with quinoline (0·15 ml.). The whole was shaken with hydrogen until 135 ml. had been absorbed at 25°/763 mm. (1H_2 = 130 ml.). There was no sign of the absorption's halting at this stage. Kieselguhr was added, the mixture filtered, the solvent evaporated, and the residue twice distilled, to give *methyl deca*-trans-2 : cis-4-*dienoate* (712 mg.). The best fraction had b. p. 75°/0·07 mm., n_D^{20} 1·4854, whilst the others had the same b. p. but n_D^{20} 1·4816—1·4854 (Found: C, 72·55; H, 10·25%). See also Table 2. It had the odour characteristic of methyl stillingate. Hydrolysis as described above gave deca-*trans*-2 : *cis*-4-dienoic acid, b. p. 122°/0·5 mm. (Found: C, 70·05; H, 9·9%). Light absorption: max. at 259 mμ (ε 16,100). The p-*bromophenacyl ester* crystallised from ethanol in needles (Found: Br, 21·2. $C_{18}H_{21}O_3Br$ requires Br, 21·85%), undepressed in m. p. by *p*-bromophenacyl stillingate. The S-*benzylthiuronium salt* crystallised from ethyl acetate (needles) (Found: N, 8·0. $C_{18}H_{26}O_2N_2S$ requires N, 8·35%): it did not depress the melting point of the corresponding stillingic derivative. The *N-iso*butylamide (see below) was identical with that from stillingic acid (infra-red spectrum). Except for the data above and in Table 2, natural deca-*trans*-2 : *cis*-4-dienoic acid was used.

Non-1-*yn*-4-*ol*.—(*a*) A Grignard reagent was prepared in dry ether (60 ml.) from magnesium etched with mercuric chloride (5·65 g.), and propargyl bromide (29·2 g.). Ether (50 ml.) was added, the mixture cooled in an ice-bath, and hexanal (22·4 g.) added slowly so that refluxing did not occur. The product was stirred for 2 hr., set aside overnight, and then decomposed by water and dilute acid. The ether layer was collected, dried, and distilled. *Non*-1-*yn*-4-*ol* was isolated, and on redistillation the major portion (8·5 g., 27%) had b. p. 107—109°/32 mm., n_D^{25} 1·4458 (Found: C, 76·8; H, 11·55. $C_9H_{16}O$ requires C, 77·1; H, 11·5%). It probably contains allenic impurity as does the specimen described below (cf. Celmer and Solomons, *J. Amer. Chem. Soc.*, 1953, **75**, 3430). This is eliminated during the Grignard carboxylation step.

(*b*) Zinc wool (70 g.) was etched with 2*N*-hydrochloric acid, washed with ethanol and ether, and covered with tetrahydrofuran (100 ml.). Mercuric chloride (50 mg.) and then a few ml. of a mixture of propargyl bromide (120 g.) and hexanal (110 g.) were added. A reaction set in promptly and the remainder of the mixture was added dropwise. When addition was complete, the product was refluxed for 2 hr. and poured into 10% acetic acid (1 l.). Sufficient sodium chloride was added to saturate the solution which was then thoroughly extracted with ether. The extracts were dried, evaporated, and distilled. Non-1-yn-4-ol (58 g., 41%), b. p. 58—60°/0·1 mm., n_D^{21} 1·4509, was obtained, together with much higher-boiling material which was not further investigated.

4-*Tetrahydropyranyloxynon*-1-*yne*.—Non-1-yn-4-ol (32·9 g.) was mixed with dihydropyran (20 g.) and cooled in ice. Phosphorus oxychloride (0·2 ml.; Henbest, Jones, and Walls, *J.*, 1950, 3646) was added, and the product set aside for 12 hr. and then poured into water, extracted with ether, and distilled. The majority (32 g.) had b. p. 71—80°/0·08 mm., $n_D^{17\cdot5}$ 1·4542—1·4598. The *ether* of b. p. 75—77°/0·08 mm., $n_D^{17\cdot5}$ 1·4543, was used for analysis (Found: C, 74·65; H, 11·1. $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%).

Methyl 5-*Hydroxydec*-2-*ynoate*.—A Grignard reagent was prepared from magnesium (12·5 g.) and ethyl bromide (55 g.) in anhydrous ether (250 ml.), 4-tetrahydropyranyloxynon-1-yne (55 g.) in anhydrous benzene (375 ml.) was added slowly, and the whole stirred for 3 hr. After 1 hour's refluxing the product was poured on solid carbon dioxide in an autoclave which was then kept sealed for 3 days. The resultant sludge was treated with methanol (500 ml.)

containing sulphuric acid (45 ml.) and set aside overnight (Henbest, Jones, and Walls, *loc. cit.*). Some ether and benzene were removed by azeotropic distillation, and the mixture was set aside for 24 hr. more. Sodium hydrogen carbonate was added and the excess removed by filtration. The filtrate was concentrated, poured into water, and extracted with ether. Evaporation and distillation gave *methyl 5-hydroxydec-2-ynoate* (27·7 g.), b. p. 112—115°/0·35 mm., n_D^{16} 1·4680 (Found: C, 66·35; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·15%). Microhydrogenation required 2·0H_2. Light absorption: no max. >215 mμ. At 215 and 320 mμ, ε was 4950 and 500 respectively.

Methyl 5-Hydroxydec-cis-2-enoate.—The acetylenic ester (19·32 g.) was hydrogenated in ethyl acetate (20 ml.) in the presence of Lindlar catalyst (5 g.); quinoline was not added. After hydrogen (1·18 l.) had been absorbed, the uptake of gas almost ceased, so more catalyst (4 g.) was added. Gas absorption continued briskly and when a total of 2·265 l. of hydrogen (15°/765 mm.) was absorbed the reaction was stopped (calc. for semihydrogenation 2·37 l. at 15°/765 mm.). The catalyst was removed, the solvent evaporated *in vacuo*, and the residue distilled, to give *methyl 5-hydroxydec-cis-2-enoate* (17·7 g.), b. p. 102—106°/0·45 mm., n_D^{18} 1·4657. A portion redistilled for analysis had b. p. 104—106°/0·4 mm., n_D^{21} 1·4646 (Found: C, 66·3; H, 10·1. $C_{11}H_{20}O_3$ requires C, 66·1; H, 10·05%). Microhydrogenation required 1·1H_2. Light absorption: no max. >217 mμ. At 217 and 237 mμ, ε was 10,000 and 1000 respectively.

Dec-2-eno-5-lactone.—Methyl 5-hydroxydec-*cis*-2-enoate (16·4 g.) was refluxed with 2N-hydrochloric acid (150 ml.) for 80 min., cooled, and extracted with ether. The extracts were washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4), and the *lactone* (12·25 g.) distilled (b. p. 86°/0·07 mm., n_D^{22} 1·4709) (Found: C, 71·4; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Microhydrogenation required 1·1H_2. Light absorption: no max. >213 mμ. At 213, 230 mμ, ε was 5050 and 1200 respectively. αβ-Unsaturated, δ-lactonic C=O, 1723 cm.$^{-1}$ (liquid film).

Deca-cis-2: trans-*4-dienoic Acid.*—Sodium (0·8 g.) was dissolved in anhydrous methanol (80 ml.), dec-2-eno-5-lactone (5·24 g.) added to the cooled reagent (20°), and the whole set aside for 90 min. The solvent was then removed *in vacuo*, water (100 ml.) added, the solution was extracted with ether, and the extracts were rejected. The solution was then acidified and the acid collected with ether. Evaporation and distillation gave deca-*cis*-2: *trans*-4-dienoic acid as a refractive and rather viscous liquid, b. p. 112—114°/0·45 mm., n_D^{18} 1·5007 (Found: C, 70·4; H, 9·8%). Light absorption: max. at 258 mμ (ε 17,500). The p-*bromophenacyl ester* crystallised from ethanol–water in shining plates (Found: Br, 22·25%). The S-*benzylthiuronium salt* crystallised from ethyl acetate (Found: N, 8·0%). *Methyl deca*-cis-2: trans-*4-dienoate* was prepared from the acid (2·8 g.) at 0° with a slight excess of diazomethane in ether; it distilled at 76—80°/0·5 mm. (2·10 g.) but was contaminated by a little volatile crystalline material. This was eliminated by cooling to 0°, pouring off the ester, and redistilling it (Found: C, 72·35; H, 10·05%). Microhydrogenation required 1·9H_2. A small quantity of material, b. p. 122°/0·5 mm., $n_D^{19\cdot5}$ 1·4766, was also isolated.

Deca-2: 4-*diynoic Acid* (with J. D. Shah).—Sodamide was prepared from liquid ammonia (2 l.) and sodium (69 g.) in the presence of ferric nitrate catalyst. The bath-temp. was adjusted to −70° and dichlorobut-2-yne (123 g.) added very slowly, to give sodiodiacetylene. Pentyl bromide (151 g.) was added and the mixture stirred overnight. Residual ammonia was allowed to evaporate and the product extracted with ether. After evaporation of the ether, crude nona-1: 3-diyne (80 g.), b. p. 50°/2 mm., n_D^{21} 1·4745, was obtained.

The diyne (24 g.) in anhydrous ether (30 ml.) was added to a Grignard reagent prepared from magnesium (6·2 g.), ethyl bromide (40 g.), and ether (100 ml.), and the mixture refluxed for 3 hr. The product was poured on solid carbon dioxide in an autoclave and the whole kept sealed for 24 hr. Two similar preparations were carried out and the products united and treated with ice-cold 15% sulphuric acid. The dark syrup was extracted with ether, and the acid extracted from this with sodium hydrogen carbonate solution. After acidification under light petroleum (b. p. 40—60°; 250 ml.), the petroleum layer was removed and the aqueous phase further extracted with light petroleum. The combined extracts were washed and dried, the solvent was removed, and the residue crystallised at low temperature from light petroleum (b. p. 40—60°) to give deca-2: 4-diynoic acid (25·1 g.), as plates, m. p. 37°. Treatment of the mother-liquors afforded further acid (7·1 g.), m. p. 35·5—37° (Found: C, 73·05; H, 7·55%; equiv., 166. Calc. for $C_{10}H_{12}O_2$: C, 73·2; H, 7·3%; equiv., 164). Microhydrogenation required 3·95H_2. The p-*bromophenacyl ester* crystallised in needles, m. p. 83° (Found: C, 59·8; H, 4·7; Br, 22·3. $C_{18}H_{17}O_3Br$ requires C, 59·85; H, 4·75; Br, 22·15%). Methyl deca-2: 4-diynoate (11·6 g.), prepared by diazomethane from the acid (15 g.), had b. p. 86/0·15 mm., n_D^{19} 1·5018, d^{22} 0·9502

(Found: C, 74·3; H, 8·05. Calc. for $C_{11}H_{14}O_2$: C, 74·15; H, 7·85%). Microhydrogenation required 3·9H_2. Light absorption of the methyl ester: max. at 226, 237, 248, 262, 278 mμ (ε 1300, 2500, 4400, 5900, 3700) [Skattebol and Sorensen, *loc. cit.*, give $\lambda_{max.}$ 226, 236, 247, 261, 277 mμ (ε 1700, 3240, 6320, 7080, 5630), b. p. 40°/0·001 mm.]. Methyl deca-2:4-diynoate showed strong C≡C vibrations at 2242 and 2218 cm.$^{-1}$; C=O stretching 1714 cm.$^{-1}$. An absorption band is present at 991 cm.$^{-1}$ (liquid film).

Methyl Deca-cis-2: cis-4-*dienoate*.—Methyl deca-2:4-diynoate (8·94 g.) was shaken in methyl acetate (25 ml.) with Lindlar catalyst (4·0 g.) and quinoline (1·6 ml.) under hydrogen until 2·20 l. at 18°/767 mm. had been absorbed (2 hr.; semihydrogenation required 2·36 l. at 18°/767 mm.). The catalyst was removed and washed with methyl acetate, and the filtrate plus washings evaporated under reduced pressure at 25°. The residue was dissolved in ether, washed with 2N-sulphuric acid and then water, and dried. Distillation gave the fractions: (1) b. p. 71—72°/0·4 mm., n_D^{18} 1·4734, microhydrogenation 1·7H_2, $\lambda_{max.}$ 263 mμ (ε 11,500) (0·75 g.); (2) b. p. 72—73°/0·4 mm., n_D^{18} 1·4769, microhydrogenation 1·87H_2, $\lambda_{max.}$ 263 mμ (ε 12,700) (3·00 g.); (3) b. p. 73—74°/0·4 mm., n_D^{18} 1·4810, microhydrogenation 2·01H_2, $\lambda_{max.}$ 263 mμ (ε 16,400) (1·97 g.); (4) 74—78°/0·4 mm., $n_D^{18\cdot5}$ 1·4865, microhydrogenation 2·06H_2, $\lambda_{max.}$ 263 mμ (ε 14,400) (1·47 g.); and (5) 78°/0·4 mm., $n_D^{18\cdot5}$ 1·4912, microhydrogenation 2·76H_2, $\lambda_{max.}$ 263 mμ (ε 14,400) (0·36 g.). Fractions (2), (3), and (4) were united (6·44 g.) and re-fractionated, the best specimen having b. p. 78°/0·6 mm., $n_D^{20\cdot5}$ 1·4848, $\lambda_{max.}$ 263 mμ (ε 16,400) (Found: C, 72·8; H, 9·85%). (All ε values are calculated by using *M* 182, though the first fraction contains some overhydrogenated material and the last underhydrogenated acetylenic materials: the presence of the latter was confirmed by infra-red spectroscopy.)

Deca-cis-2: cis-4-*dienoic Acid*.—The ester (1·33 g.) was refluxed for 90 min. with a slight excess of alcoholic potassium hydroxide (the ester became yellow immediately on addition of the cold reagent), then poured into water, and the acid extracted and purified in the normal way. It had b. p. 112—114°/0·5 mm., n_D^{17} 1·4896 (0·98 g.) (Found: C, 70·4; H, 9·9%). Light absorption: max. at 260 mμ (ε 13,000). The p-*bromophenacyl ester* crystallised in plates from ethanol (Found: Br, 21·9%). The S-*benzylthiuronium salt* crystallised from ethyl acetate in plates (Found: N, 8·05%).

Hydrogenation of the Methyl Decadienoates.—The methyl ester was completely hydrogenated in methanol, in presence of palladium–barium sulphate. After filtration, the ester was hydrolysed with a slight excess of methanolic potassium hydroxide and then neutralised. *p*-Bromophenacyl bromide was added and the derivative prepared in the usual way. In all four cases *p*-bromophenacyl decanoate was obtained, having m. p. and mixed m. p. 65—66°.

Isolation of Methyl Stillingate from Stillingia Oil.—Stillingia oil ("Processed Oil," from Messrs. Couper, Friend and Co., London; raw oil has also been used) had the light absorption max. at 258, 266, 280 mμ ($E_{1\,cm.}^{1\%}$ 69, 69, 50). The oil (619 g.) was refluxed for 5 hr. with potassium hydroxide (135 g.) in methanol (700 ml.), and about half of the methanol removed by distillation. The residue was acidified with hydrochloric acid, diluted with water, and extracted with ether. These extracts were dried (Na_2SO_4) and evaporated and the crude fatty acids esterified by refluxing 1% methanolic sulphuric acid (500 ml.) for 4 hr. The product was poured into water and the mixed esters were isolated by ether-extraction, washed with dilute sodium hydroxide solution, and, after removal of the ether, fractionated. Methyl stillingate (18·6 g.) was obtained. For data see Table 2 (Found: C, 72·6; H, 10·1. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 10·0%). Microhydrogenation required 2·05H_2. A second sample isolated by this procedure had $\lambda_{max.}$ 264 mμ (ε 21,000). Crossley and Hilditch (*loc. cit.*) give b. p. 86°/0·2 mm., $\lambda_{max.}$ 264 mμ (ε 24,000). The ester had a characteristic and rather unpleasant odour.

Stillingic Acid.—Methyl stillingate (4·17 g.) was refluxed with methanolic potassium hydroxide (45 ml.; 0·837N) for 60 min. The ester rapidly became yellow but not dark. Most of the methanol was distilled and an excess of water was added. The acid was isolated by acidification (Congo-red) and ether-extraction: it was purified by dissolution in sodium hydroxide solution (10%), the free acid being collected with ether after acidification. Drying (Na_2SO_4), evaporation in nitrogen, and distillation yielded stillingic acid (2·73 g.) as a viscous colourless liquid, b. p. 107°/0·2 mm., n_D^{18} 1·5078 (Found: C, 70·85; H, 9·65%). Microhydrogenation required 1·98H_2. Light absorption: max. at 257 mμ (ε 18,000). A second specimen had $\lambda_{max.}$ 257 mμ (ε 19,300). The acid was highly unstable, and in air at 25° during 12 hr. a film polymerised to gum. Its p-*bromophenacyl ester* crystallised in flat needles from ethanol–water (Found: Br, 21·8%). This had partly resinified after 14 days at 0°. The S-*benzylthiuronium salt* formed powdery prisms from ethyl acetate (Found: N, 8·3%).

Deca-2: 4-*dienols*.—These were prepared by slowly adding a solution of lithium aluminium

hydride in ether to a solution of the appropriate methyl ester in ether, at such a rate that ether did not reflux. Excess of reagent was decomposed by water, ice-cold dilute sulphuric acid was added, and the ether layer separated, evaporated, and distilled.

trans-2 : trans-4-*Dienol*. Methyl deca-*trans*-2 : *trans*-4-dienoate (0·47 g.) was reduced with lithium aluminium hydride (0·079 g.) to give *deca*-trans-2 : trans-4-*dienol* (0·34 g.) (Found : C, 77·65; H, 11·95. $C_{10}H_{18}O$ requires C, 77·85; H, 11·75%). The α-*naphthylurethane* formed fluffy needles from light petroleum (b. p. 40—60°) (Found : N, 4·35. $C_{21}H_{25}O_2N$ requires N, 4·35%).

trans-2 : cis-4-*Dienol*. The ester (0·96 g.) and lithium aluminium hydride (0·12 g.) gave the *dienol* (0·60 g.) (Found : C, 77·4; H, 11·9%). The α-*naphthylurethane* crystallised from light petroleum (b. p. 40—60°) as needles (Found : N, 4·35%). It was markedly more soluble in petroleum than the *trans*-2 : *trans*-4-isomer, as were the *cis*-2 : *trans*-4- and *cis*-2 : *cis*-4-compounds. The *p*-phenylazobenzoyl derivative was an oil.

cis-2 : *trans*-4-*Dienol*. The ester (1·06 g.) gave, with lithium aluminium hydride (0·15 g.), *deca*-cis-2 : trans-4-*dienol* (0·79 g.) (Found : C, 77·65; H, 11·85%).

cis-2 : *cis*-4-*Dienol*. Methyl deca-*cis*-2 : *trans*-4-dienoate (0·88 g.) and lithium aluminium hydride (0·11 g.) yielded *deca*-cis-2 : cis-4-*dienol* (0·58 g.) (Found : C, 77·9; H, 11·75%). The α-*naphthylurethane* was recrystallised three times from light petroleum (b. p. 40—60°) (Found : N, 4·45%).

Preparation of iso*Butylamides*.—The acid (1 mol.) in benzene was treated with excess of oxalyl chloride (usually 1·3 mol.) at 25°. After 2 hr., the mixture was heated under reflux for 1 hr., and the solvent and excess of reagent were removed *in vacuo*. The acid chloride was distilled and dissolved in anhydrous ether. *iso*Butylamine (2·5 mol.) in ether was added dropwise with cooling and shaking. After 1 hr. the product was poured into water, washed with N-sulphuric acid, then sodium hydrogen carbonate solution, dried, evaporated, and distilled. N-iso*Butyldeca*-trans-2 : trans-4-*dienamide* (0·964 g.), m. p. 90° (Found : C, 75·2; H, 11·6; N, 6·4. $C_{14}H_{25}ON$ requires C, 75·25; H, 11·3; N, 6·25%), was obtained from the acid (1·00 g.) by the above procedure but replacing the distillation by crystallisation at 0° from light petroleum (b. p. 40—60°) gave needles (microhydrogenation : $1·9H_2$). See also Table 4. Deca-*trans*-2 : *cis*-4-dienoic acid (1·63 g.) gave the iso*butylamide* (1·62 g.) as an almost colourless viscous liquid (Found : C, 75·0; H, 11·25; N, 6·3%. Microhydrogenation : $2·0H_2$). The *cis*-2 : *trans*-4-acid (0·91 g.) gave its iso*butylamide* (0·80 g.) according to the general method (Found : C, 75·5; H, 11·4; N, 6·0%. Microhydrogenation : $1·9H_2$). Similarly the *cis*-2 : *cis*-4-acid (0·58 g.) gave the corresponding iso*butylamide* (0·49 g.) (Found : N, 6·1%).

N-iso*Butyldeca*-trans-2-*en*-4-*ynamide* (1·7 g. : Found : C, 75·65; H, 10·45; N, 6·5%. Microhydrogenation : $2·9H_2$. $C_{14}H_{23}ON$ requires C, 75·95; H, 10·5; N, 6·35%) was prepared from the corresponding acid (1·53 g.). It was not distilled and after two recrystallisations (with charcoaling) from light petroleum (b. p. 40—60°) formed needles, m. p. 69°. Light absorption : max. at 258 mμ (ε 21,500).

N-iso*Butyl*-trans-2 : trans-4-*sorbamide* (Found : C, 71·8; H, 10·2; N, 8·2. Microhydrogenation : 1·95. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·25; N, 8·35%) crystallised in short needles or plates, m. p. 112°, from light petroleum (b. p. 40—60°)–benzene. Light absorption : max. at 257 mμ (ε 31,500). *N-iso*Butyl-*trans*-2 : *trans*-4-sorbamide is inactive against adult *Tenebrio molitor* and *Musca domestica*. It is desirable to keep all unsaturated *iso*butylamides at 0° in sealed tubes. Those containing *cis*-linkages are the most unstable, but pure specimens of *N-iso*butyl-*trans*-2 : *trans*-4-sorbamide and *N-iso*butyldeca-*trans*-2 : *trans*-4-dienamide changed to a brown gum in air at 25° during about 14 days. The deterioration may happen overnight but in other cases may be long delayed.

Reaction Between Stereoisomeric iso*Butylamides and Maleic Anhydride*.—*N-iso*Butyldeca-*trans*-2 : *trans*-4-dienamide (100 mg.), maleic anhydride (40 mg.), and benzene (0·8 ml.) were sealed under nitrogen and heated at 100° for 90 min. On cooling to 25°, a solid product crystallised. Heating was continued for 5 hr. in all and, after cooling, the *adduct* was filtered off and crystallised (needles, m. p. 193° somewhat dependent on rate of heating) from benzene (Found : C, 66·95; H, 8·25; N, 4·4. $C_{18}H_{27}O_4N$ requires C, 67·25; H, 8·45; N, 4·35%). The three stereoisomeric *iso*butylamides were examined in a similar way but no crystalline products were obtained.

Iodine-catalysed Irradiation.—The three methyl deca-2 : 4-dienoates containing *cis*-linkages were dissolved in light petroleum (b. p. 40—60°), and a trace of iodine was added. The *cis*-2 : *cis*-4-compound retained a slight pink-purple colour; the *cis*-2 : *trans*-4- and the *trans*-2 : *cis*-4-compound became pale brown, the former also becoming turbid. The solutions in thin glass test-tubes, were irradiated overnight with a "Hanovia" ultra-violet lamp, then washed

with dilute aqueous sodium thiosulphate and water, dried, and evaporated. Their infra-red spectra (liquid films) were then examined and no appreciable change had occurred in any case. The experiments were repeated in quartz tubes with the same results.

Thermal Treatment.—Specimens of the four methyl deca-2 : 4-dienoates were sealed in tubes from which the air was not displaced and heated at 160—180° for 45 min. As judged by development of colour the *cis*-2 : *cis*-4- and the *cis*-2 : *trans*-4-stereoisomer had deteriorated most (orange-brown). The *trans*-2 : *cis*-4-form was pale yellow but the colour of the *trans*-2 : *trans*-4-form was unaltered. Their infra-red spectra showed that no appreciable stereomutation had occurred.

Infra-red Spectra.—These (cf. Figs. 2 and 3) were measured on a Grubb-Parsons single-beam instrument with rock-salt optics (see Part I for further details). The author is much indebted to Dr. W. C. Price for these facilities.

The spectra of the stereoisomeric *N-iso*butyldeca-2 : 4-dienamides are tabulated below. For abbreviations, see Part III. All samples are liquid films except the *trans*-2 : *trans*-4-amide (paraffin mull).

trans-2 : *trans*-4. 3295 ms, 3075 mw, 2898 s, 2709 w, 1654 s, 1625 s, 1614 s, 1550 s, 1457 s, 1374 s, 1338 m, 1311 mw, 1260 m (i), 1254 m, 1207 mw, 1187 w, 1159 m, 1126 w, 1066 w, 1038 w, 994 s, 943 mw, 920 w, 890 w, 875 m, 856 w, 843 w, 818 mw, 737 mw, 722 mw, 681 mw cm.$^{-1}$.

trans-2 : *cis*-4. 3285 ms, 3076 mw, 2957 s, 2937 s, 2867 s, 1653 s, 1623 s, 1609 ms, 1549 s, 1466 s, 1389 mw, 1368 mw, 1328 m, 1272 m, 1210 mw, 1157 mw, 1101 w, 993 ms, 963 m, 923 w, 870 m, 819 w, 775 m, 729 w cm.$^{-1}$.

cis-2 : *trans*-4. 3285 ms, 3090 w, 2960 s, 2930 s, 2865 ms, 1650 s, 1632 s, 1605 ms, 1546 s, 1464 ms, 1436 ms, 1395 mw, 1369 mw, 1341 w, 1302 w, 1262 ms, 1231 ms, 1270 w, 1156 mw, 1126 w, 1086 w, 998 m, 961 m, 932 w, 922 w, 876 w, 858 w, 823 m, 811 m (i), 729 w cm.$^{-1}$.

cis-2 : *cis*-4. 3285 ms, 3075 mw, 2945 s, 2924 s, 2860 ms, 1720 w, 1649 s, 1628 s, 1595 ms (i), 1546 s, 1466 ms, 1436 m, 1387 mw, 1370 mw, 1340 mw, 1327 mw (i), 1270 m, 1252 m, 1215 mw, 1169 mw, 1157 m, 1126 w, 1101 mw, 994 m, 962 m, 920 w, 911 mw, 824 m, 726 w cm.$^{-1}$.

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Amides of Vegetable Origin. Part VI. Synthesis of Capsaicin.*

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An unambiguous synthesis of capsaicin, *N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-*trans*-6-enamide, the active principle of red pepper, is described.

Various species of the genus *Capsicum* (for recent taxonomic information see Heiser and Smith, *Economic Botany*, **1953**, **7**, 214) contain in their fruits (red peppers) an intensely sharp and pungent substance, capsaicin, which was first isolated by Thresh (*Pharm. J. and Trans.*, 1876—7, [iii], **7**, **21**, **259**, **473**; 1877—8, **8**, 187). Miko (*Z. Nahr. Genussm.*, 1898, **1**, 818; 1899, **2**, 411) obtained it pure and crystalline (m. p. 63·5°) and recognised a phenolic hydroxyl and a methoxyl grouping. Its formulation as *N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide is due to Nelson (*J. Amer. Chem. Soc.*, **1919**, **41**, 1115, 1472; 1920, **42**, 597; 1923, **45**, 2179; contrast Lapworth and Royle *J.*, **1919**, 1109). Its synthesis was claimed by Späth and Darling (*Ber.*, 1930, **63**, 737), the essential steps in the preparation of the intermediate 8-methylnon-6-enoic acid being as shown. As would be expected from this type of synthesis, a mixture of acids (presumably containing structural and geometrical isomers) was obtained from the quinoline dehydrohalogenation. The mixture could not be resolved by distillation or crystallisation but by a tedious

* Part V, preceding paper.

purification through the *N*-(3 : 4-dimethoxybenzyl)amide the acid was obtained sufficiently pure to establish identity of its *N*-(4-hydroxy-3-methoxybenzyl)amide with capsaicin.

The aims of the present work were, first, diagnosis of the configuration of capsaicin and then synthesis by an unambiguous stereospecific method. Capsaicin was isolated from capsicin oleoresin by a method similar to that of Lapworth and Royle (*loc. cit.*),

$$Me_2CH{\cdot}CH_2{\cdot}ZnI + Cl{\cdot}CO{\cdot}[CH_2]_4{\cdot}CO_2Et \longrightarrow Me_2CH{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_4{\cdot}CO_2H \xrightarrow[EtOH]{Na-}$$

$$Me_2CH{\cdot}CH_2{\cdot}CH(OH){\cdot}[CH_2]_4{\cdot}CO_2H \xrightarrow{HBr,\ 100^\circ} Me_2CH{\cdot}CH_2{\cdot}CHBr{\cdot}[CH_2]_4{\cdot}CO_2H \xrightarrow[200-220^\circ]{Quinoline}$$

$$Me_2CH{\cdot}CH{=}CH{\cdot}[CH_2]_4{\cdot}CO_2H + \text{other isomers}$$

though final purification was effected by chromatography. Its infra-red spectrum showed a medium-strong band at 968·5 cm.$^{-1}$, indicative of a *trans*-double bond in a molecule of this type (cf. Part V), and a synthetical method was chosen for this isomer.

2 : 3-Dichlorotetrahydropyran was treated with *iso*propylmagnesium bromide. The 3-chlorotetrahydro-2-*iso*propylpyran thus produced reacted with powdered sodium giving,

$$Me_2CH{\cdot}MgBr + Cl{\cdot}CH{\cdot}CHCl{\cdot}[CH_2]_2{\cdot}CH_2 \longrightarrow Me_2CH{\cdot}CH{\cdot}CHCl{\cdot}[CH_2]_2{\cdot}CH_2 \xrightarrow{Na}$$
(O)

$$Me_2CH{\cdot}CH{=}CH{\cdot}[CH_2]_2{\cdot}OH \xrightarrow{PBr_3} Me_2CH{\cdot}CH{=}CH{\cdot}[CH_2]_2{\cdot}Br \xrightarrow[synthesis]{Malonic} Me_2CH{\cdot}CH{=}CH{\cdot}[CH_2]_4{\cdot}CO_2H$$

after fractionation from a contaminant of low b. p., 6-methylhept-*trans*-4-en-1-ol, the configuration being based on previous experience of this reaction (Crombie and Harper, *J.*, 1950, 1707; Crombie, *J.*, 1952, 2997) and on the infra-red spectrum; the alcohol has not shown any indications of heterogeneity. On ozonolysis it gave *iso*butyraldehyde.

Conversion of 6-methylhept-*trans*-4-en-1-ol into its bromide, followed by a malonate reaction, completed the synthesis of 8-methylnon-*trans*-6-enoic acid, the carbon skeleton of which was proved by hydrogenation to the known 8-methylnonanoic acid. 8-Methylnon-*trans*-6-enoic acid was converted into its acid chloride and thence into the desired amide, which was identical with natural capsaicin. It had the characteristic intensely sharp taste, detectable in extreme dilution, and gave a positive test with vanadium oxychloride in carbon tetrachloride (Fodor, *Kiserlet Kozlemenyek*, 1930, **33**, 155; cf. *Chem. Abs.*, 1931, **25**, 2780). Dihydrocapsaicin was also prepared from the 8-methyl nonanoic acid described above.

Experimental

Analyses were carried out in the microanalytical laboratories of Imperial College (Mr. F. H. Oliver). Ultra-violet light absorptions were measured in ethanol with a Hilger medium quartz instrument (Mrs. I. Boston).

Natural Capsaicin.—This was isolated from capsicin oleoresin by a modification of Lapworth and Royle's procedure (*loc. cit.*) : after chromatography on alumina and recrystallisation, it formed leaflets, m. p. 64°, from 9 : 1 light petroleum (b. p. 40—60°)–ether. Light absorption : max. at 227, 281 mμ (ε 7000, 2500). The infra-red spectrum (paraffin mull) showed bands (*inter alia*) at 3320 (NH broadened as it overlies the OH), 3090, 1650 (C=C), 1629 (amide A, C=O), 1598 (Ph_I), 1553 (amide B), 1511 (Ph_{II}), 1454, 1429, 1372, 1349, 1282, 1241, 1201, 1172, 1155, 1121, 1032, 968·5, 937·5, 843, 809, 718 cm.$^{-1}$. Assignments are tentative.

6-*Methylhept*-trans-4-*en*-1-*ol.*—*iso*Propylmagnesium bromide was prepared from magnesium (96 g.) and *iso*propyl bromide (480 g.) in ether (1 l.). The reagent was cooled in ice-water, and 2 : 3-dichlorotetrahydropyran solution [prepared by addition, during 12 hr., of the theoretical amount of chlorine to dihydropyran (252 g.) in ether (600 ml.) at 0—7°] was slowly added with stirring. Towards the end of the addition, solid may separate and stirring become difficult. Excess of Grignard reagent was destroyed with ammonium chloride solution, and as much of the ether layer as possible decanted. The residue was decomposed with dilute hydrochloric acid (this caused some formation of tar). This solution was extracted with ether, and the united ethereal extracts were washed with sodium hydrogen carbonate solution

and dried (K_2CO_3). Evaporation and distillation yielded crude 3-chlorotetrahydro-2-*iso*propylpyran (mixture of stereoisomers) which was collected between 65° and 110°/12 mm. (n_D^{21} 1·4592). In 4 experiments the yields were 31, 33, 36, and 38%.

The crude product (165 g.) was added slowly to powdered sodium (65 g.) covered by anhydrous ether (cf. Crombie and Harper, *J.*, *loc. cit.*). The product was treated with methanol and then water, and the ether layer separated. The aqueous phase was extracted with ether, and the united extracts were evaporated and distilled. A small fore-run was rejected and the main product (86·5 g.) had b. p. 53—58°/12 mm., n_D^{20} 1·4429. This was united with a batch of similar material (56·6 g.) obtained from 3-chlorotetrahydro-2-*iso*propylpyran (148 g.) and fractionated through a gauze-packed Stedman column (3 ft.). After elimination of low-boiling material (48·6 g.; b. p. 37—38°/14 mm., n_D^{23} 1·4354) (Found: C, 73·9, 74·3; H, 12·1, 12·3%), *6-methylhept*-trans-*4-en*-*1-ol* (63·2 g.), b. p. 87°/14 mm., n_D^{21} 1·4430 (Found: C, 74·65; H, 12·55. $C_8H_{16}O$ requires C, 75·0; H, 12·6%), was obtained. Ozonolysis of the latter yielded *iso*butyraldehyde, isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 181°. The *p-diphenylylurethane*, crystallised from light petroleum (b. p. 40—60°), had m. p. 99° (Found: C, 77·3; H, 7·75. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·8%).

6-Methylhept-trans-*4-enyl Bromide*.—Phosphorus tribromide (12·0 g.) was added slowly to the *trans*-alcohol (16·0 g.) and pyridine (3·5 ml.), with stirring at 0° which was maintained for 30 min., and the crude *bromide* was distilled directly. It was dissolved in light petroleum (b. p. 40—60°), washed with dilute sodium hydroxide solution and then water, dried, and redistilled (12·3 g.). It had b. p. 68—73°/13 mm., n_D^{25} 1·4690 (Found: C, 49·9; H, 8·1; Br, 40·7. $C_8H_{15}Br$ requires C, 50·45; H, 7·9; Br, 41·5%).

8-Methylnon-trans-*6-enoic Acid*.—A solution of ethyl sodiomalonate was prepared from sodium (2·7 g.), ethanol (80 ml.), and ethyl malonate (19·0 g.). 6-Methylhept-*trans*-4-enyl bromide (23 g.) was added dropwise with stirring and the mixture refluxed for 2 hr.; as much alcohol as possible was then removed on a steam-bath. The residual crude alkenylmalonic ester was refluxed with aqueous potassium hydroxide for 3 hr., then cooled and acidified (Congo-red). Extraction with ether gave the alkenylmalonic acid which was decarboxylated at 160—180° (2 hr.). The resulting acid was dissolved in dilute aqueous sodium hydroxide, and the solution extracted with ether. After acidification of the aqueous phase the pure acid was collected with ether, dried (Na_2SO_4), and distilled. *8-Methylnon*-trans-*6-enoic acid* (10·7 g., 52%), b. p. 130—132°/12 mm., n_D^{22} 1·4460, was obtained (Found: C, 70·25; H, 10·55. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·65%). The *p-bromophenacyl ester* crystallised from ethanol in needles, m. p. 64° (Found: C, 58·85; H, 6·5. $C_{18}H_{23}O_3Br$ requires C, 58·85; H, 6·3%).

8-Methylnonanoic Acid.—The above acid (800 mg.) was hydrogenated in dioxan, with Adams platinum catalyst, until absorption of gas ceased (110 ml. of H_2 at 20°/750 mm.: Calc., 114 ml.). The catalyst was removed, the solvent evaporated, and the acid distilled (b. p. 100—102°/3 mm., n_D^{24} 1·4352) (Found: C, 69·35; H, 11·7. Calc. for $C_{10}H_{20}O_2$: C, 69·7; H, 11·7%). Its amide had m. p. 103—104°. Levene and Allen (*J. Biol. Chem.*, 1916, **27**, 462) give m. p. 103°.

N-(*4-Hydroxy-3-methoxybenzyl*)-*8-methylnon*-trans-*6-enamide*.—4-Hydroxy-3-methoxybenzylamine hydrochloride, prepared by Nelson's method (*J. Amer. Chem. Soc.*, 1919, **41**, 1115) in 51% yield, had m. p. 214° (from ethanol). The free base was dried at 100° before use and had m. p. 132°.

8-Methylnon-*trans*-6-enoic acid (1·04 g.) was treated with thionyl chloride (1·3 mol.) and set aside for 18 hr. at 20°. It was then heated at 100° for 30 min. and excess of reagent removed under reduced pressure. The residual acid chloride, in ether (10 ml.), was added to the freshly prepared amine (1·8 g.; finely divided) suspended in ether (50 ml.). This mixture was shaken for 3 days and then poured into water and extracted. The extracts were dried and evaporated to yield the crude *amide* (1·49 g.) which crystallised from light petroleum (b. p. 40—60°)–ether in colourless leaflets, m. p. 65°, undepressed on admixture with natural capsaicin (Found: N, 4·45. $C_{18}H_{27}O_3N$ requires N, 4·6%). Crystallisation is made difficult by a tendency to form oils. Light absorption: max. at 227, 280 mμ (ε 8200, 2700). The infra-red spectrum (700—1300 cm.$^{-1}$) was identical with that of natural capsaicin reported above.

The *N*-(4-hydroxy-3-methoxybenzyl)amide of 8-methylnonanoic acid (0·45 g.) was prepared similarly from the acid (0·37 g.) and amine (0·33 g.). It had m. p. 64—65°. Nelson (*J. Amer. Chem. Soc.*, 1923, **45**, 2179) gives m. p. 65° for the product of hydrogenation of natural capsaicin.

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The Constitution and Stereochemistry of Terrein.

By D. H. R. Barton and E. Miller.

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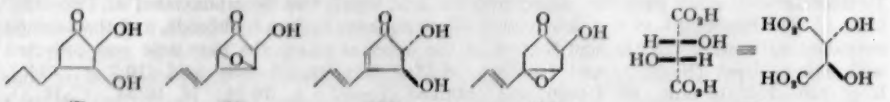
The constitution of the mould metabolite terrein has been elucidated. The stereochemistry of the molecule has been established by conversion into a derivative of (+)-tartaric acid.

The mould metabolite terrein was first isolated by Raistrick and Smith (*Biochem. J.*, 1935, **29**, 606). In an extensive and elegant contribution Raistrick and his collaborators (Clutterbuck, Raistrick, and Reuter, *ibid.*, 1937, **31**, 987) established that tetrahydroterrein, easily obtained by catalytic hydrogenation of terrein, had the constitution (I). Since terrein gives acetaldehyde on ozonolysis an ethylenic linkage must be placed in the *n*-propyl side chain. Of the various possible constitutions for terrein which remain, the interesting formula (II) was given preference. It seemed to us that the recorded chemical facts also made formulæ (III) and (IV) worthy of consideration. The former was one of the structures favoured by Raistrick *et al.*, but tentatively rejected on the grounds that terrein failed to react with maleic anhydride. However, one must note that the conjugated diene system of (III) would be deactivated towards dienophils of the usual type because of the conjugated carbonyl group.

With the very kind encouragement of Professor H. Raistrick, F.R.S., we have obtained additional evidence which confirms the correctness of (III). Terrein showed (in ethanol)



$\lambda_{max.}$ 275 (ε 26,000) and 342 mμ (ε 130), a spectrum characteristic of conjugated dienones such as (III). In the infra-red region terrein exhibited maxima at 3620 and 3420 (hydroxyl), at 1700, 1640, and 1575 (·CO·C:C·C:C·, the CO being placed in a five-membered ring) and at 967 cm.$^{-1}$ (*trans*-CH:CH·), the spectrum being in complete agreement with formula (III).

That terrein contains two hydroxyl groups was demonstrated as follows. Terrein 2 : 4-dinitrophenylhydrazone (Clutterbuck, Raistrick, and Reuter, *loc. cit.*), which showed the ultra-violet absorption spectrum expected of a conjugated dienone derivative, gave a diacetate on treatment with pyridine and acetic anhydride at room temperature. 2 : 4-Dinitrophenylhydrazones are not, of course, acetylated on nitrogen under these conditions (see Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 5309). In the infra-red region (bromoform solution) the diacetate showed bands at 3350 (NH), 1742 and 1225 (acetate; strength of bands indicative of two acetate residues), and 967 cm.$^{-1}$ (*trans*-CH:CH·), in agreement with the assigned constitution. Both terrein and its 2 : 4-dinitrophenylhydrazone are stable in pyridine solution at room temperature.

On the basis, particularly, of the work already cited (Raistrick *et al.*, *loc. cit.*) and of the additional facts recorded above, the constitution (III) for terrein may be taken as established. The same conclusion has also been reached by Grove (personal communication; *J.*, 1954, 4693) on the basis, mainly, of spectroscopic evidence. We cordially thank Mr. J. F. Grove for sending us a copy of his manuscript.

The stereochemistry of terrein, both relative and absolute, has been elucidated as follows. The *trans*-configuration of the side-chain ethylenic linkage is shown by the infra-red data cited above. The *trans*-relation of the two hydroxyl groups, already made probable by the failure of terrein 2 : 4-dinitrophenylhydrazone to consume periodic acid, was proved by controlled ozonolysis of acetylated terrein. Conversion of the acidic product

into the di-*p*-bromophenacyl ester gave the di-*O*-acetyl-(+)-tartaric acid derivative identical with authentic material. The isolation of this derivative of (+)-tartaric acid (V) (Bijvoet, Peerdeman, and van Bommel, *Nature*, 1951, **168**, 271) proves that terrein has the stereochemistry already indicated in (III). It also, incidentally, provides further confirmation for the proposed constitution.

Experimental

Unless stated to the contrary, ultra-violet absorption spectra were determined in $CHCl_3$ with the Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories using the same solvent unless stated to the contrary. Rotations were likewise determined in $CHCl_3$ solution.

Terrein 2 : 4-Dinitrophenylhydrazone Diacetate.—Terrein 2 : 4-dinitrophenylhydrazone (Clutterbuck, Raistrick, and Reuter, *loc. cit.*), $[\alpha]_D$ −619° (*c*, 0·06), $\lambda_{max.}$ 400 mμ (ε 33,700) (85 mg.), in acetic anhydride (1 ml.) and pyridine (2 ml.) was left at room temperature for 14 hr. Crystallisation of the product from ethyl acetate–methanol gave *terrein 2 : 4-dinitrophenylhydrazone diacetate*, m. p. 195—196°, $[\alpha]_D$ −613° (*c*, 0·53), $\lambda_{max.}$ 391 mμ (ε 38,700) [Found : C, 51·5; H, 4·3; Ac (determined by alkaline hydrolysis followed by distillation from aqueous sulphuric acid), 18·25. $C_{18}H_{18}O_8N_4$ requires C, 51·65; H, 4·35; Ac, 20·6%].

Di-p-bromophenacyl Di-O-acetyl-(+)-tartrate.—Di-*O*-acetyl-(+)-tartaric anhydride (216 mg.) in 50% ethanol (10 ml.) was neutralised with aqueous potassium hydroxide, and the solution refluxed with *p*-bromophenacyl bromide (556 mg.) for 2 hr. Crystallisation of the product from chloroform–methanol gave *di-p-bromophenacyl di-O-acetyl-(+)-tartrate*, m. p. 175—176°, $[\alpha]_D$ −9·3° (*c*, 2·46) (Found : C, 45·6; H, 3·2; Br, 25·8. $C_{24}H_{20}O_{10}Br_2$ requires C, 45·9; H, 3·2; Br, 25·4%). On crystallisation from methanol the ester melts (Köfler block) at 159—161° (plates) and then at 175—176° (needles).

Conversion of Terrein into Di-O-acetyl-(+)-tartaric Acid.—Terrein (250 mg.) was treated with acetic anhydride (1·0 ml.) and pyridine (2·0 ml.) for 14 hr. at room temperature. The resultant diacetate, which did not crystallise, was ozonised in carbon tetrachloride (100 ml.) at −20° for 2½ hr. (the optimum time was determined by preliminary experiments). The solution was warmed on the steam-bath for 30 min. and then titrated with aqueous 0·87N-potassium hydroxide (phenolphthalein) (3 equivs. required 5·6 ml.; consumed, 5·8 ml.). The aqueous layer was separated and hydrogen peroxide (30%; 2 ml.) added. After 10 min. the peroxide was destroyed by the addition of platinum. The filtered solution was evaporated *in vacuo* at pH 7 and the residue dissolved in 50% ethanol (20 ml.) and treated with *p*-bromophenacyl bromide (1·38 g.) as above. Crystallisation of the product from chloroform–methanol gave di-*p*-bromophenacyl di-*O*-acetyl-(+)-tartrate (54 mg.) identified by m. p., mixed m. p., rotation {$[\alpha]_D$ −8·7° (*c*, 2·24)} and infra-red spectrum. Crystallisation from methanol gave the second crystal form (plates; m. p. and mixed m. p.) referred to above.

We are much indebted to Professor H. Raistrick, F.R.S., for generously supplying us with terrein. We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial support, and Dr. P. de Mayo for very helpful assistance.

Birkbeck College, London, W.C.1. [*Received, November 18th*, 1954.]

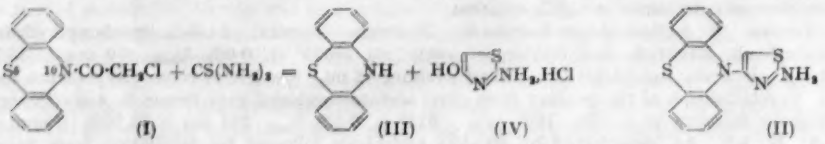
The Preparation of Some Heterocyclic Sulphur Compounds as Possible Anthelmintics.

By Alexander Mackie and Anand L. Misra.

[Reprint Order No. 5709.]

The following observations were made during attempts to prepare a variety of heterocyclic sulphur compounds for use as anthelmintics.

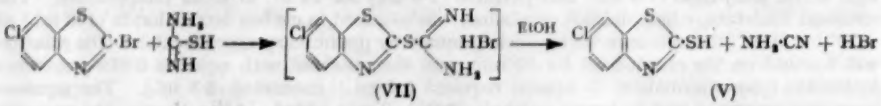
10-Chloroacetylphenothiazine (I) was treated with thiourea with the view to obtain 2-amino-4-10′-phenothiazinylthiazole (II). Phenothiazine (III) and 2-amino-4-hydroxythiazole hydrochloride (IV) were isolated. It is possible that the hydrochloride of (II) was



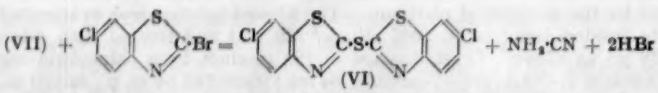
(I) (III) (IV) (II)

first formed, and was then immediately hydrolysed by ethanolic hydrochloric acid to (III) and (IV) (cf. Maly, *Ber.*, 1877, **10**, 1853; Davies, Maclaren, and Wilkinson, *J.*, 1950, 3493; Ziegler, *J. Amer. Chem. Soc.*, 1941, **63**, 2946; Sprague, Land, and Ziegler, *ibid.*, 1946, **68**, 2155). When the order of addition of the reactants was reversed, a small quantity of 10-acetylphenothiazine was isolated in addition to (III) and (IV).

Next, 2-bromo-6-chlorobenzothiazole with thiourea was found to give 6-chloro-2-mercaptobenzothiazole (V) in good yield in ethanol and di-(6-chloro-2-benzothiazolyl) sulphide (VI) in very poor yield in water. This affords a good method for the preparation of 6-substituted 2-mercaptobenzothiazoles, which are otherwise obtained laboriously from



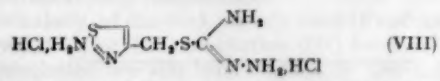
(VII) (V)



(VI)

6-amino-2-mercaptobenzothiazole. These observations substantiate the previous findings by Scott and Watt (*J. Org. Chem.*, 1937, **2**, 148) and Watt (*ibid.*, 1939, **4**, 436). According to the mechanism postulated by these authors, the formation of (V) presumably depends on the formation of an unstable intermediate addition compound (VII), which decomposes into 6-chloro-2-mercaptobenzothiazole in ethanol, and reacts in water, owing to greater ionisation, with an additional molecule of 2-bromo-6-chlorobenzothiazole to form (VI), according to the annexed scheme.

Finally, 2-amino-4-chloromethylthiazole hydrochloride condensed with thiosemicarbazide to form an *S*-substituted thiosemicarbazide (VIII) (cf. Sprague, Land, and Ziegler, *loc. cit.*).



(VIII)

The results of the biological testing of the benzothiazoles and of the thiazolyl derivatives will be published elsewhere.

Experimental.—Reaction of 10-chloroacetylphenothiazine with thiourea. 10-Chloroacetylphenothiazine (Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302) (11·5 g.) was added to a boiling ethanolic solution (40 c.c.) of thiourea (3 g.). The mixture was refluxed for 3 hr.; plates separated, which were filtered off, washed with hot ethanol, and dried (12·5 g.). Washing with cold acetone removed the phenothiazine formed in the reaction, and the residue (5 g.), on recrystallisation

from methanol, gave colourless prisms of 2-amino-4-hydroxythiazole hydrochloride (IV) (4 g.), m. p. 206—208° (decomp.) (Found: C, 24·1; H, 3·3. Calc. for $C_3H_5ON_2ClS$: C, 23·6; H, 3·3%). When the order of the addition of the reactants in this reaction was reversed, phenothiazine and 10-acetylphenothiazine, m. p. 198—199°, were isolated, along with (IV).

Addition of pyridine to the hot saturated aqueous solution of the hydrochloride liberated the base, which was obtained pure on recrystallisation from water as colourless needles, becoming light brown at 220°, dark brown at 234°, m. p. 242—244° (decomp.) (Found: C, 30·9; H, 3·3. Calc. for $C_3H_4ON_2S$: C, 31·0; H, 3·4%); it reduced Fehling's solution. The base has been reported by King and Miller (*J. Amer. Chem. Soc.*, 1949, **71**, 367) who give m. p. 233—238° (decomp.), and by Davies, Maclaren, and Wilkinson (*J.*, 1950, 3491) who give m. p. 230—240° (decomp.). No depression of the m. p. was observed on admixture with the tautomeric ψ-thiohydantoin, m. p. 241—243° (Allen and VanAllan, *Org. Synth.*, 1947, **27**, 72). The benzylidene derivative of the base obtained above sinters at 280° and has m. p. 294° (decomp.), which was not depressed when mixed with benzylidene-ψ-thiohydantoin (cf. Kucera, *Monatsh.*, 1914, **35**, 137; Stieger, *ibid.*, 1916, **37**, 653; Culvenor, Davies, Maclaren, Nelson, and Savige, *J.*, 1949, 2573).

2-Bromo-6-chlorobenzothiazole. This *compound*, prepared from 2-amino-6-chlorobenzothiazole (Kaufmann and Schulz, *Arch. Pharm.*, 1935, **273**, 22) (20 g.) by Elderfield and Short's method (*J. Org. Chem.*, 1953, **18**, 1092) for the preparation of 2-bromo-4-chlorobenzothiazole, formed dark yellow needles (16·5 g.) (from ethanol), m. p. 97—98° (Found: C, 33·8; H, 1·1. $C_7H_3NClBrS$ requires C, 33·8; H, 1·2%).

6-Chloro-2-mercaptobenzothiazole (V). 2-Bromo-6-chlorobenzothiazole (2·5 g.) was added to a hot saturated ethanolic solution of thiourea (0·75 g.). The red solution was refluxed for 4 hr. on the water-bath. The separated product was collected and recrystallised from aqueous ethanol in clusters of pale yellow needles (1·5 g.), m. p. 250—252° (Found: C, 41·6; H, 2·0. Calc. for $C_7H_4NClS_2$: C, 41·7; H, 2·0%). Teppema and Sebrell (*J. Amer. Chem. Soc.*, 1927, **49**, 1779) give m. p. (not sharp) 245°, and Drozdov and Stavrovskaya (*J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2813) m. p. 244—245°. The preparation by Sandmeyer reaction from 6-amino-2-mercaptobenzothiazole is reported in both papers.

Di-(6-chloro-2-benzothiazolyl) sulphide (VI). 2-Bromo-6-chlorobenzothiazole (2·5 g.) was added to a boiling aqueous solution of thiourea (0·75 g. in 15 c.c.), and the mixture refluxed on the water-bath for 4 hr. The pale yellow solid, which separated, was filtered off, shaken with cold 10% aqueous sodium hydroxide (150 c.c.), and collected. The residue was washed with water and recrystallised from chlorobenzene–light petroleum (b. p. 40—60°) as light brown needles of the *sulphide* (0·3 g.), m. p. 174—176° (Found: C, 45·9; H, 2·0; N, 7·4; S, 25·6. $C_{14}H_6N_2Cl_2S_3$ requires C, 45·5; H, 1·6; N, 7·6; S, 26·0%). 2-Bromo-6-chlorobenzothiazole (1·5 g.) was recovered.

S-(2-Amino-4-thiazolylmethyl)thiosemicarbazide dihydrochloride (VIII). 2-Amino-4-chloromethylthiazole hydrochloride (Sprague, Land, and Ziegler, *J. Amer. Chem. Soc.*, 1946, **68**, 2155) (5 g.) was added to a boiling 70—80% ethanolic solution (30 c.c.), of thiosemicarbazide (2·5 g.), and the mixture refluxed for 2 hr. on the water-bath. A vigorous reaction set in when complete dissolution was effected and a crystalline precipitate separated, which was collected after cooling and recrystallised from aqueous methanol in colourless prisms of the pure substituted *thiosemicarbazide dihydrochloride* (4·5 g.), m. p. 211—212° (vigorous decomp.), becoming light brown at 195° (Found: C, 21·8; H, 3·9; N, 26·2. $C_5H_{11}N_5Cl_2S_2$ requires C, 21·7; H, 4·0; N, 25·4%). The base, liberated from an aqueous solution of the hydrochloride on addition of slight excess of potassium acetate or pyridine, crystallised from water in colourless plates, m. p. 173—174° (decomp.).

p-Dimethylaminobenzaldehyde S-(2-amino-4-thiazolylmethyl)thiosemicarbazone. A hot ethanolic solution of *p*-dimethylaminobenzaldehyde (0·3 g. in 5 c.c.) was added to a hot aqueous-ethanolic solution (20 c.c.) of the above thiosemicarbazide hydrochloride (0·3 g.) and sodium acetate (0·35 g.). The mixture was refluxed on the water-bath for 2 hr. The separated product was cooled, collected, and recrystallised from absolute ethanol as greyish prismatic needles of the *thiosemicarbazone* (0·25 g.), m. p. 207—208° (decomp.) (Found: C, 50·3; H, 5·2. $C_{14}H_{19}N_6S_3$ requires C, 50·3; H, 5·4%).

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HERIOT-WATT COLLEGE, EDINBURGH. [*Received, September 6th*, 1954.]

The Stability of the Three-co-ordinated Thiourea Silver Complex.

By W. S. Fyfe.

[Reprint Order No. 4846.]

Thiourea forms a stable complex ion with the silver ion in aqueous solution and as there are very few data on the stability of silver complexes with sulphur as the donor atom the formation constant of this complex has been measured. Morgan and Burstall (*J.*, 1928, 143) prepared a series of complexes with one, two, three, and four mols. of thiourea to one of silver.

When thiourea is added to a silver nitrate solution a precipitate which is first formed dissolves when the molar ratio of thiourea to silver is approximately 3 : 1. The formation of the complex was studied electrometrically at 25° with a simple concentration cell :

$$Ag|0{\cdot}1\text{M-}AgNO_3|2\text{M-}NH_4NO_3|AgNO_3(c_1)\text{–}CS(NH_2)_2(c_2)|Ag$$

The activity coefficients used in the calculation of the formation constants were taken from McInnes (*Chem. Rev.*, 1936, **18**, 341). The values used were 0·734, 0·844, 0·97 for 0·1M-, 0·01M-, and 0·001M-silver nitrate respectively. It was assumed that the activity coefficients of the complex were the same as for silver nitrate. The experimental results are summarised in the Table, E being the e.m.f. of the cell and $K = [AgTu_3^+]/[Ag^+][Tu]^3$, where Tu = thiourea. From the reasonable constancy of log K the three-co-ordinated

c_1 (M)	c_2 (M)	E	log K	c_1 (M)	c_2 (M)	E	log K
0·001	0·1963	0·761	13·13	0·001	0·02334	0·574	12·90
,,	0·1167	0·713	13·01	0·01	0·1191	0·644	13·11
,,	0·0805	0·686	13·05	,,	0·0953	0·624	13·16
,,	0·0744	0·680	13·05	,,	0·0595	0·560	13·06
,,	0·0584	0·659	13·01	,,	0·0584	0·558	13·06

Mean, log K = 13·05.

complex appears to be stable over the limited concentration range studied. The complex is also one of the more stable silver complexes—more stable than the ammonia complexes, in agreement with expectations from overlap calculations made by the author (*J. Chem. Phys.*, 1952, **8**, 1039), the stability of the sulphur–metal linkage in complexes being a function of the low electron-affinity of sulphur.

The co-ordination number of three which has been found with thiourea is unusual for silver complexes, two being usual for aqueous solution. The explanation may lie in the configuration of the sulphur atom in thiourea. The sulphur atom may be in either an sp or sp^2 hybrid state as it forms both a σ- and a π-bond with carbon. If the configuration is sp, then as the sulphur atom approaches the silver ion it may form a σ-bond with a sp hybrid orbital but it still has a p-orbital in a position to form a π-bond if silver has some suitable orbital available. If the hybridisation is sp^2, then the silver can either form a σ-bond with the thiourea which will make the Ag–S–C bond angular, or it can interact and form two weak bonds with both sp^2 hybrids, the Ag–S–C bond being linear. Both these cases involve the use of d-orbitals from the silver atom. A further possibility which involves no d orbital hybridisation is that the silver atom forms a trigonal planar grouping with the three sulphur atoms with a sp^2 silver hybrid and that the remaining silver p-orbital will form a resonating π-bond with the sulphur p-orbitals. The structure would be analogous to that in the carbonate ion. Finally, it is possible that d sulphur orbitals may be involved, as suggested by the results of Craig, Maccoll, Nyholm, Orgel, and Sutton (*J.*, 1954, 332).

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The Thermal Decomposition of Ammonium Dichromate.

By Duncan Taylor.

[Reprint Order No. 5803.]

For the thermal decomposition of ammonium dichromate with continuous evacuation in the temperature range 188—218°, Fischbeck and Springler (*Z. anorg. Chem.*, 1939, **241**, 209) reported that after an induction period t' the fraction decomposed at any time t is proportional to $(t - t')^4$, up to about 30% decomposition (approximately the maximum-rate stage), as required by a linear growth of spherical nuclei whose number increases linearly with time. From about 30 to 100% decomposition, a contracting-sphere type of mechanism applied, governed by the equation $1 - (1 - x)^{\frac{1}{3}} = \text{const.}\ (t - t_0)$, where x is the fraction decomposed, and t_0 is the time at which the maximum rate occurred. Reinvestigation of the decomposition without employing continuous evacuation has revealed new features of the kinetics, and an alternative mechanism is proposed.

Experimental and Results.—Decompositions were carried out at 195—218° in an apparatus similar to that of Garner and Haycock (*Proc. Roy. Soc.*, 1952, *A*, **211**, 338) with the addition, between the reaction vessel and expansion bulbs, of a trap (P_2O_5) to remove water vapour. The pressure of the remaining nitrogen was measured with a Macleod gauge placed after the expansion bulbs. The reaction-vessel temperature was controlled within ±0·05° by an electric furnace and electronic relay, and was measured with a Pallador thermocouple, which was calibrated against a platinum resistance thermometer. Small crystals (0·1—0·2 mm.) of ammonium dichromate, obtained by rapid crystallisation of " AnalaR " material at 30—40°, were used in 5—14 mg. quantities in a closed vessel constructed from 2 cm.² of 0·025-mm. thick platinum foil. The thermocouple indicated a maximum heating-up period of about 5 min., and gave no evidence of self-heating of the crystals during decomposition. Before decomposition, samples were degassed for 3—4 hr. at room temperature and a pressure less than 10^{-6} mm., no significant difference in rates being observed with 18 hours' evacuation. The total volume of the system was 6200 c.c.

Typical pressure–time curves are given in Fig. 1, zero time being the moment when the sample reached the hot zone of the reaction vessel. The maximum rate in the autocatalytic stage occurred in all cases at about 20% decomposition, calculated on the basis of the scheme, $(NH_4)_2Cr_2O_7 \rightarrow Cr_2O_3,H_2O + 3H_2O + N_2$ (Fischbeck and Springler, *Z. anorg. Chem.*, 1938, **235**, 183), and had a temperature coefficient corresponding to an energy of activation of 33 kcal./mole (see Fig. 2, line *A*). Irrespective of temperature, this stage was complete after about 45% decomposition, and was followed by a constant-rate stage over the range 45—65% decomposition, with an energy of activation of 38 kcal./mole (see Fig. 2, line *B*). Both the maximum rate and the constant rate were directly proportional to the initial weight of the sample and were reproducible to within 10%. Following the constant-rate process, the pressure increased in an irregular manner and, depending on the temperature, the maximum decomposition even after several days' heating was only 75—85%. Induction periods (defined as the time required for the pressure to reach 10^{-3} mm.) varied from 2 to 15 min., but in general decreased with increasing temperature. Slight grinding of the crystals did not significantly alter the rates at any stage, but prolonged grinding resulted in the disappearance of the induction period and in increased irreproducible rates, the maximum of which occurred very early.

Discussion.—The results differ from those of Fischbeck and Springler in the following respects: (*a*) the occurrence of the maximum rate earlier in the decomposition; (*b*) the occurrence of a constant-rate stage, indicating a linear interface reaction (cf. Jacobs and Tompkins, *Proc. Roy. Soc.*, 1952, *A*, **215**, 273); and (*c*) failure to attain 100% decomposition at any temperature. Furthermore, it has been found that for the initial stages of the decomposition the equation $x = (t - t')^n$ fits the present results only approximately, n varying between 2 and 3, and that the equation of the contracting-sphere mechanism fits moderately well only from 45 to 70% decomposition, the corresponding energy of activation being about 35 kcal./mole, in contrast to 49 kcal./mole found by Fischbeck and Springler. These differences are thought not to be due to the different experimental conditions because (*a*) in both cases the pressure of

residual water vapour is estimated to be $<10^{-4}$ mm., and (*b*) experiment showed that the decomposition of single crystals (about 8 mg.) was unaffected by the presence initially of 0·06 mm. pressure of nitrogen.

The autocatalytic stage can best be represented by the Prout–Tompkins equation, $\log_{10} p/(p_f - p) = \text{constant} + k \log_{10} t$ (*Trans. Faraday Soc.*, 1944, **40**, 488; 1946, **42**, 468), with a single value of k instead of the usual two values, when the final pressure p_f (estimated by trial and error) corresponds to the conclusion of the stage (see Fig. 2, line *C*). The use of the experimental pressures in the equation involves the assumption either that the interface reaction is insignificant during the autocatalytic stage, or that the pressure due to the latter process at any time

FIG. 1.

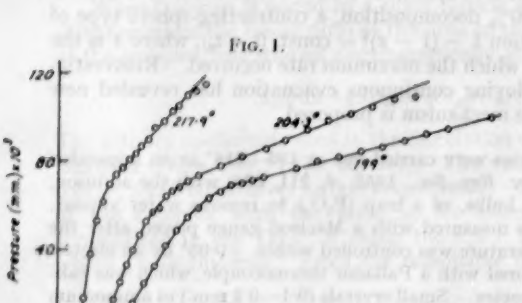
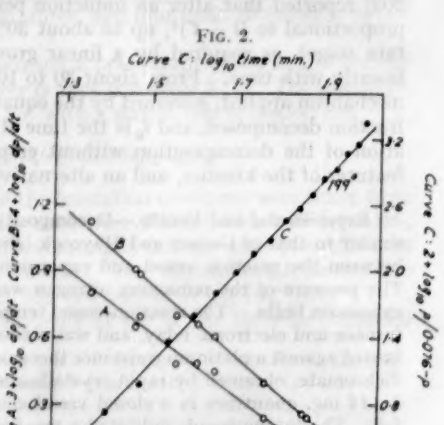


FIG. 2.



is a constant fraction of the total. The agreement of the results with the equation is in keeping with the fact that during decomposition the ammonium dichromate lattice probably undergoes changes (as judged from the lattice dimensions of dichromate and chromic oxide) similar to those for permanganates, for whose decomposition the Prout–Tompkins mechanism was originally proposed. The need for a single value of k is unusual, but may be due to the completion of the autocatalytic stage at only about 45% decomposition. The fit of the equation was less satisfactory if allowance was made for the short induction periods, and furthermore, although the maximum rate varied regularly with temperature (see Fig. 2, line *A*), the variation of k with temperature was erratic. For the first 5% of the decomposition, the equation did not apply satisfactorily, and this fact taken in conjunction with the occurrence of induction periods suggests that a nucleation process may precede the autocatalytic stage.

UNIVERSITY OF EDINBURGH. [*Received, October* 14*th*, 1954.]

Decomposition of Mixed Diazonium Fluoroborates.

By J. C. Brunton and H. Suschitzky.

[Reprint Order No. 5806.]

In an unsuccessful attempt to improve the low yields attending the preparation of *o*-fluoronitrobenzene by a Balz–Schiemann reaction (Roe, "Organic Reactions," John Wiley and Sons, New York, 1949, Vol. V, p. 220), we modified the usual decomposition method: *o*-nitrobenzenediazonium fluoroborate was mixed in one series of experiments (*a*) with a diazonium fluoroborate of a negligible conversion yield, and in another (*b*) with a fluoroborate of a high conversion yield, in various proportions. We considered that this arrangement should increase the total concentration of the fluorinating agent, whatever its nature, for each of the constituents, and thereby possibly affect the yields. *p*-Carboxybenzenediazonium fluoroborate was intended for use under (*a*) because the synthesis of *p*-fluorobenzoic acid *via* this intermediate is recorded as unsuccessful (Dippy and Williams, *J.*, 1934, 1466). However, repeating the preparation, we obtained the acid in 40% yield (based on the fluoroborate), and this is, therefore, more convenient than the usual method (Schiemann and Winkelmüller, *Org. Synth.*, Vol. II, p. 299). The reported failure may have been due to the high solubility of this fluoroborate in water.

On the basis of the experimental results obtained so far (see Table) it appears that diazonium fluoroborates in admixture decompose without appreciable interaction.

The mixed decomposition method has preparative advantages. It was found convenient for the simultaneous preparation of two separable aromatic fluorine compounds. Moreover, a mildly decomposing fluoroborate proved to be an ideal diluent in the decomposition of diazonium fluoroborates containing the nitro-group, since it transforms the otherwise violent pyrolysis into a smooth reaction.

Decomposition of *o-nitrobenzenediazonium fluoroborate in admixture with similar fluoroborates*, $R{\cdot}N_2BF_4$.

$R{\cdot}N_2BF_4$	Molar ratio, $R{\cdot}N_2BF_4/o\text{-}NO_2{\cdot}C_6H_4{\cdot}N_2BF_4$	RF: Yield, %, alone	RF: Yield, %, mixed	$o\text{-}C_6H_4F{\cdot}NO_2$: Yield, %, alone	$o\text{-}C_6H_4F{\cdot}NO_2$: Yield, %, mixed
o-Toluene	1·5	50—60	56	10—12	11
,,	5·5	,,	60	,,	10
,,	7·0	,,	60	,,	12·6
2 : 4-Dinitrobenzene	0·5	negl.	negl.	,,	11·5
p-Carboxybenzene	0·5	40	38	,,	10

Experimental.—No diluent was used for the decompositions, which were carried out under nitrogen (Suschitzky, *J.*, 1953, 3042). The mixtures were prepared by co-precipitating the fluoroborates from the combined solutions of the corresponding diazotised amines.

p-*Fluorobenzoic acid.* The method of Dippy and Williams (*loc. cit.*) yielded *p*-carboxybenzenediazonium fluoroborate (80%), decomp. 89°. The salt was only washed with ether. Decomposition produced the acid as a white sublimate (40%), m. p. 185° (Found: equiv., 141. Calc. for $C_7H_5O_2F$: equiv., 140).

2 : 4-*Dinitrobenzenediazonium fluoroborate.* 2 : 4-Dinitroaniline (25 g., 0·14 mol.), dissolved in concentrated sulphuric acid (150 c.c.) and water (200 c.c.), was diazotised with 30% sodium nitrite solution. Addition of a 40% sodium fluoroborate solution (25 g.) yielded the pale yellow fluoroborate (92%, 35·7 g.), decomp. 208°. Only traces of 1-fluoro-2 : 4-dinitrobenzene, identified by mixed m. p. with an authentic sample, were obtained by pyrolysis.

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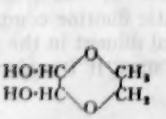
An Addition Compound of Glyoxal and Ethylene Glycol.

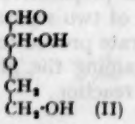
By Frank S. H. Head.

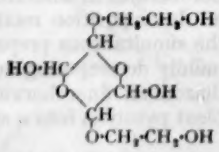
[Reprint Order No. 5823.]

It is well known that glyoxal and ethylene glycol in the presence of hydrochloric acid give a mixture of isomeric cyclic acetals commonly known as the naphthodioxans, but it does not seem to have been reported that a 1 : 1 compound of the semiacetal type is formed under milder conditions. This was obtained as a crystalline, water-soluble substance in 70—80% yield when an aqueous solution of glyoxal and ethylene glycol in equimolecular proportion was evaporated to dryness at room temperature *in vacuo*. When heated, it melted and decomposed, giving off a greenish-yellow vapour (presumably monomeric glyoxal). It was only slightly soluble in most organic solvents; in hot xylene it gave a yellow solution which became colourless again on cooling.

Structures such as (II), containing carbonyl groups, are excluded by absence of absorption at 1920—1520 cm.$^{-1}$. The bis-semiacetal structure (I), and polymeric structures such as (III) or its dioxolan analogue [which might be formed by way of (II)], are possible. The infra-red spectrum is not inconsistent with formula (I) since it exhibits (*a*) a broad, intense, absorption band at 3600—3000 cm.$^{-1}$, typical of associated hydroxyl groups, and (*b*) certain similarities to the spectrum of dioxan, *viz.*, bands near 1270 and 1250 and (very intense) between 1130 and 980 cm.$^{-1}$.


(I)


(II)


(III)

The structure (I) accords with the formation of 2 : 3-dichlorodioxan on treatment with phosphorus pentachloride, but in view of the drastic nature of the treatment this evidence may not be conclusive. Hydrolysis of the dichloro-compound with boiling water gave a solution from which the supposed dihydroxy-compound could be recovered, but it is possible that the hydrolysate contained glyoxal and glycol (cf. Böeseken, Tellegen, and Henriquez, *Rec. Trav. chim.*, 1931, **50**, 909), and that these combined during the working-up.

The behaviour of the substance in aqueous solution was consistent with its formulation as a cyclic semiacetal, which might be expected to dissociate to some extent into the open-chain form (II), and then into the original components: with phenylhydrazine in acetic acid it gave an immediate precipitate of glyoxal bisphenylhydrazone, and recognised methods for the determination of glyoxal could be used to determine the amount present in the substance.

On oxidation with sodium metaperiodate, a compound (I) should reduce one mol. of periodate and give one mol. of glycol diformate. A compound (II) should also reduce one mol. of periodate, but would give one mol. of formic acid and one of glycol monoformate. A mixture of one mol. each of glyoxal and glycol should reduce two mols. of periodate very rapidly and yield two mols. each of formic acid and formaldehyde. The tabulated results (*a*) (given as mole/mole) show a very rapid initial reduction of about one mol. of periodate with formation of much formic acid (but $\ll$1 mol.) and a small amount of formaldehyde;

	(*a*) 0·025M-$C_4H_8O_4$ in 0·0734M-$NaIO_4$			(*b*) 0·025M-$(CH_2{\cdot}O{\cdot}CHO)_2$ in 0·050M-$NaIO_4$		
Time	15 mins.	1 day	22 days	1 day	5 days	21 days
Periodate reduced	1·04	1·13	1·97	0·00	0·18	0·97
Acid produced ...	0·68	0·94	2·02	0·10	0·89	1·95
CH_2O produced ...	0·10	0·24	2·00	—	0·44	2·00

subsequent reduction of periodate was very slow, but after about three weeks approximated to oxidation of a 1 : 1 mixture of glyoxal and glycol. The figures for a reaction time of 15 minutes are consistent with the view that the crystalline substance is (I), but that, in

solution, it exists in equilibrium with a certain amount of (II), and of the original components. The products of oxidation would then include glycol mono- and di-formate, and the slowness of the subsequent reaction could be attributed to the slow hydrolysis of these esters [cf. Table (*b*)] : liberation of acid from glycol diformate preceded commencement of oxidation, but very little appeared during the first 24 hours, making it unlikely that the formic acid observed during the early stages of the oxidation of the substance arises from hydrolysis of glycol diformate.

With an excess of glycol containing hydrochloric acid, the substance gave rise to the mixture of " naphthodioxans " previously obtained by other methods, including the reaction of glycol with 2 : 3-dichlorodioxan (Böeseken *et al.*, *loc. cit.*).

Experimental.—The addition compound (2 : 3-*dihydroxydioxan* ?). (*a*) A mixture of glycol (45·4 g.) and commercial 50% glyoxal (83·9 g.) was kept *in vacuo* over phosphoric oxide until it had mostly solidified (about a week). The solid *substance* was separated from syrup by mixing it with acetone and filtering (68 g., 77%). It formed colourless crystals from acetone (Found : C, 39·9; H, 6·3. $C_4H_8O_4$ requires C, 40·0; H, 6·7%). The " available " glyoxal in the substance was determined by oxidation with (i) alkaline hydrogen peroxide (Friedemann, *J. Biol. Chem.*, 1927, **73**, 331) and (ii) alkaline hypoiodite (cf. Head, *J. Text. Inst.*, 1947, **38**, T 389) [Found : (i) 48·5; (ii) 48·0. Calc. for $(CHO)_2$–$(CH_2{\cdot}OH)_2$: 48·3%]. The glycol was determined as follows. The substance was heated for 10 min. with an excess of sodium hydroxide solution (to convert glyoxal into glycollic acid), and the solution neutralised with hydrochloric acid (cf. Friedemann, *loc. cit.*) and oxidised with an excess of sodium metaperiodate for 15 min. Formaldehyde produced was determined by the dimedone method (cf. Head and Hughes, *J.*, 1952, 2046) (Found : 52·0. $C_4H_8O_4$ requires CH_2O, 51·7%). The substance melted indefinitely at about 100°. The infra-red absorption was measured with the dry solid, which was placed between rock-salt plates, melted, and quickly solidified to a glass-like film.

(*b*) 2 : 3-Dichlorodioxan (7·1 g.) was boiled under reflux with water (25 c.c.) until all the oil had dissolved (a few minutes). The cold solution was treated with sodium hydrogen carbonate until only faintly acid to Congo-red and evaporated to dryness at room temperature *in vacuo* over phosphoric oxide. Extraction of the residue with hot acetone and concentration of the extract yielded a substance (2·75 g., 51%) identical with that obtained from glyoxal and glycol.

2 : 3-*Dichlorodioxan from the addition ocmpound*. The compound (31 g.) was added in three portions to phosphorus pentachloride (111 g.). When the vigorous reaction had abated, the mixture was heated on the steam-bath for 15 min. and then cooled. The liquor was filtered from unchanged phosphorus pentachloride, and phosphorus oxychloride was removed *in vacuo* (Widmer column). The remaining oil was dissolved in benzene, washed with water, dried ($CaCl_2$), and fractionated. A fraction, b. p. 71—75°/9 mm. (21·8 g.), consisted of 2 : 3-dichlorodioxan, m. p. 29° (54%), and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 30°. A fraction, b. p. 93—94°/9 mm. (6 g.), was not identified.

Periodate oxidation of the addition compound, and of ethylene glycol diformate. The reaction mixtures were kept in the dark in a thermostat at 20°. For details of the analytical methods used to determine formic acid and formaldehyde, see Head and Hughes (*loc. cit.*). In view of the anomalies observed when variants of the arsenite method are used to determine periodate in the presence of partially oxidised glucose (Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941; Head and Hughes, *J.*, 1954, 603) the amount of periodate reduced by the addition compound was determined both by an arsenite method (Müller and Friedberger, *Ber.*, 1902, **35**, 2652) and by reduction with iodide in acid solution; the two methods agreed. The arsenite method was used in the experiments with glycol diformate.

" *Naphthodioxans*." A mixture of the addition compound (4 g.) and dry glycol (10 c.c.) containing about 0·5% of hydrogen chloride was heated on the steam-bath for 21 hr. Colourless needles (0·9 g.) which separated on cooling were recrystallised from methanol, and had m. p. 135° alone, or mixed with the higher-melting " naphthodioxan " (Böeseken *et al.*, *loc. cit.*). The glycol filtrate contained material of m. p. about 90°, which appeared to be the difficultly separable eutectic mixture of the higher- and lower-melting forms described by earlier workers.

The author is indebted to Dr. M. M. Davies of Aberystwyth for determining the infra-red absorption spectra.

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The Interaction of Calcium Ions with Some Citrate Buffers: A Correction.

By C. W. Davies and B. E. Hoyle.

[Reprint Order No. 5830.]

Some calculations of our earlier paper on this topic (*J.*, 1953, 4134) are regrettably in error. Schubert and Lindenbaum's value for the dissociation constant of the $CaCit^-$ ion (*J. Amer. Chem. Soc.*, 1952, **74**, 3529) is $7{\cdot}0 \times 10^{-4}$ at ionic strength 0·16, and on correction to zero ionic strength this becomes $2{\cdot}1 \times 10^{-5}$ (and not $1{\cdot}27 \times 10^{-5}$ as given in our paper). This affects all our calculations of calcium–citrate interaction, and the following Table should replace Table 2 of our former paper (all concentrations are in millimoles/l.).

M	*S*	pH, buffer	pH, sat. soln.	$[CaH_2Cit^+]$	[CaHCit]	$[CaCit^-]$	*I*	$K \times 10^5$ (CaHCit)
			A. Disodium hydrogen citrate solution					
5·0	9·20	5·48	4·53	0·04	1·85	1·11	0·0288	0·80
10·0	10·61	5·32	4·57	0·06	3·23	2·20	0·0372	0·81
20·0	13·30	5·20	4·64	0·08	5·03	4·22	0·0584	0·81
			B. Na_2HCit (0·9M) + HCl (0·1M)					
5·0	8·98	5·18	4·41	0·04	1·71	0·77	0·0285	0·79
10·0	10·15	5·18	4·45	0·07	3·03	1·53	0·0359	0·79
20·0	12·32	5·17	4·51	0·11	4·73	3·02	0·0543	0·84
			C. Na_2HCit (0·8M) + HCl (0·2M)					
5·0	8·77	4·90	4·27	0·05	1·51	0·48	0·0281	0·75
10·0	9·66	4·84	4·32	0·09	2·47	1·05	0·0352	0·90
20·0	11·36	4·80	4·36	0·15	4·12	1·99	0·0509	0·91
			D. Na_2HCit (0·5M) + HCl (0·5M)					(CaH_2Cit^+)
10·0	8·53	3·85	3·60	0·12	0·77	0·06	0·0326	85
20·0	9·08	3·85	3·57	0·23	1·31	0·09	0·0427	85
40·0	10·04	3·77	3·56	0·51	2·19	0·15	0·0629	68

The concordance of the results is improved, and the constants determined are now:

$CaCit^- \rightleftharpoons Ca^{2+} + Cit^{3-}$; $K = 2{\cdot}1 \times 10^{-5}$ $\quad$ $CaHCit \rightleftharpoons CaCit^- + H^+$; $K = 1{\cdot}6 \times 10^{-6}$

$CaHCit \rightleftharpoons Ca^{2+} + HCit^{2-}$; $K = 8{\cdot}1 \times 10^{-4}$ $\quad$ $CaH_2Cit^+ \rightleftharpoons CaHCit + H^+$; $K = 1{\cdot}7 \times 10^{-3}$

$CaH_2Cit^+ \rightleftharpoons Ca^{2+} + H_2Cit^-$; $K = 0{\cdot}08$

Heinz (*Biochem. Z.*, 1951, **321**, 314) has derived values for the dissociation constants of $CaCit^-$ and CaHCit by electrometric titrations of citric acid in the presence of calcium chloride. His values are considerably lower than those given above. He attributed the whole anomaly in the later stages of the titration to the species $CaCit^-$, however, and similarly he ignored $CaCit^-$ in calculating the dissociation constant for CaHCit. The detailed analysis of the above Table shows that this is not justifiable; the concentrations of CaHCit and $CaCit^-$ are approximately equal in disodium hydrogen citrate solutions, and to ignore one will lead to too low a calculated dissociation constant for the other.

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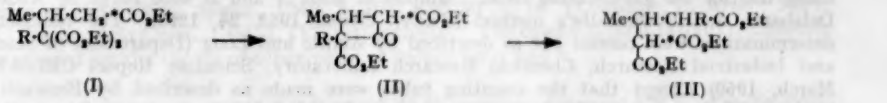
The "Abnormal" Michael Addition.

By G. A. SWAN.

[Reprint Order No. 5851.]

REACTION between diethyl methylmalonate and ethyl crotonate in the presence of a catalytic amount of sodium ethoxide yields the normal addition product, triethyl 2-methylbutane-1 : 3 : 3-tricarboxylate (I; R = Me), but in the presence of a molecular amount of catalyst the abnormal product, triethyl 2-methylbutane-1 : 1 : 3-tricarboxylate (III; R = Me) results. Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4598) assumed the partition of the diethyl methylmalonate into methyl and diethoxycarbonylmethyl radicals; but Holden and Lapworth (*J.*, 1931, 2368) suggested the more plausible explanation of the formation of an intermediate (II) by Dieckmann cyclisation, followed by ring-opening to give (III). More recent work has not, however, provided direct evidence of the correctness of the latter theory (Gardner and Rydon, *J.*, 1938, 48; Tsuruta, Yasuhara, and Furukawa, *J. Org. Chem.*, 1953, **18**, 1246).

If, however, one carried out the reaction with ethyl [*carboxy*-^{14}C]crotonate, hydrolysed the ester to the tricarboxylic acid, and then decarboxylated the latter, from the normal product one should obtain inactive, and from the abnormal product radioactive carbon



(I) (II) (III)

dioxide, if Holden and Lapworth's theory is correct. (If Michael and Ross's theory is correct, inactive carbon dioxide should result in both cases.) A preliminary experiment along these lines (but with ethyl [*carboxy*-^{14}C]cinnamate) had already shown the essential correctness of Holden and Lapworth's theory, when the results of similar experiments on the crotonate were published by Simamura, Inamoto, and Suehiro (*Bull. Chem. Soc. Japan*, 1954, **27**, 221). In view of that publication, further work has been abandoned.

The participation of (II) as an intermediate has been questioned, because of the four-membered ring. However, the driving force of the abnormal reaction is the greater acid strength of (III; R = Me) compared with (I; R = Me), and an experiment was carried out in support of this. In the addition of diethyl malonate to ethyl crotonate, the same product (I; R = H or III; R = H) is obtained regardless of the amount of sodium ethoxide used. If, however, [*carboxy*-^{14}C]crotonate is used, then if the first-formed product (I; R = H: giving acid *A* on saponification) did in fact undergo cyclisation and ring opening as in the case where R = Me, one should obtain radioactive carbon dioxide on decarboxylation of the resulting tricarboxylic acid (*B*). It was demonstrated that this carbon dioxide was virtually inactive, showing that the abnormal mechanism does not operate when the above-mentioned driving force is absent.

Radioactivity of carbon dioxide (counts/min.)

By combustion of acid A	2230	By decarboxylation of acid A	0
" " " B	2230	" " " B	28
Calc. value for the latter if complete randomisation occurred	3900		

In the experimental section is recorded the preparation of three acids apparently not previously prepared by the Michael reaction.

Experimental.—Ethyl [carboxy-^{14}C]*crotonate.* This was prepared (in contrast to that of the Japanese workers) as follows. Barium [^{14}C]carbonate was converted into potassium [^{14}C-]cyanide by McCarter's method (*J. Amer. Chem. Soc.*, 1951, **73**, 483) and thence into [*carboxy*-^{14}C-]malonic acid (Gal and Shulgin, *ibid.*, p. 2938) and into [*carboxy*-^{14}C]crotonic acid (Letch

and Linstead, *J.*, 1932, 454), which was esterified with ethanol in the presence of sulphuric acid.

Reaction between ethyl [carboxy-^{14}C]*crotonate and diethyl malonate in the presence of a catalytic amount of sodium ethoxide.* Diethyl malonate (4·1 g.), and then ethyl [*carboxy*-^{14}C]crotonate (2·7 g.) were added to a solution of sodium ethoxide [from sodium (0·09 g.)] in ethanol (2 ml.) and ether (30 ml.), and the solution was refluxed for 5 hr., cooled, and shaken with water (2 ml.) containing acetic acid (0·4 ml.). The ethereal layer was washed with sodium carbonate solution, dried (K_2CO_3) and distilled twice, yielding triethyl 2-methylpropane-1 : 1 : 3-[3-*carboxy*-^{14}C]tricarboxylate (5·5 g.), b. p. 145°/1·5 mm. (Found : C, 57·0; H, 8·35. Calc. for $C_{12}H_{22}O_6$: C, 56·95; H, 8·05%). This ester (0·35 g.) was refluxed for 10 hr. with sodium hydroxide solution (7 ml.; 10%), the mixture cooled, acidified (HCl), and extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue recrystallised from acetone–chloroform, affording the tricarboxylic acid *A* [0·1 g.; m. p. 136° (decomp.)] (Found : C, 44·35; H, 5·5. Calc. for $C_7H_{10}O_6$: C, 44·2; H, 5·25%).

Action of sodium ethoxide (1 *mole*) *on the ester.* The ester (2·7 g.) was added to a suspension of alcohol-free sodium ethoxide [from sodium (0·23 g.)] in ether (50 ml.), and the resulting solution was refluxed for 8 hr. When worked up as before, this yielded an ester (1·95 g.; b. p. 140°/1 mm.) (Found : C, 57·05; H, 8·35%) which on being hydrolysed yielded the tricarboxylic acid *B*, m. p. 136° (decomp.) (Found : C, 43·9; H, 5·5%).

Radioactivity determinations. Samples of acids *A* and *B* were decarboxylated by being heated in a vacuum, the resulting carbon dioxide being passed through a spiral trap, cooled in solid carbon dioxide, and collected in a trap cooled in liquid nitrogen, before transfer to the filling line for the gas-counting tube. Samples of acids *A* and *B* were burnt by Anderson, Delabarre, and Bothner-By's method (*Analyt. Chem.*, 1952, **24**, 1298). The radioactivity determinations were carried out as described by Audric and Long (Department of Scientific and Industrial Research, Chemical Research Laboratory, Scientific Report CRL/AE 51, March, 1950) except that the counting tubes were made as described by Brownell and Lockhart (Laboratory for Nuclear Science and Engineering, M.I.T., Technical Report No. 30, Sept. 12th, 1949).

Butane-1 : 3 : 3-*tricarboxylic acid.* Diethyl methylmalonate (4·8 ml.) was added to sodium ethoxide [from sodium (0·11 g.)] in ethanol (2·2 ml.) and ether 45 ml.); ethyl acrylate (3·3 ml.) was then added cautiously, and the mixture refluxed for 2·5 hr. Worked up as above, this yielded triethyl butane-1 : 3 : 3-tricarboxylate (5·6 g.; b. p. 145°/3 mm.) (Found : C, 57·15; H, 8·05. Calc. for $C_{12}H_{22}O_6$: C, 56·95; H, 8·05%) (von Auwers, *Annalen*, 1896, **292**, 209, gives b. p. 164·5—165°/15 mm.) which on hydrolysis yielded the acid as plates, m. p. 134° (decomp.), from acetone–chloroform (Found : C, 44·25; H, 5·3. Calc. for $C_7H_{10}O_6$: C, 44·2; H, 5·25%) (Wieland and Vocke, *Z. physiol. Chem.*, 1928, **177**, 71, give m. p. 134°).

Propane-1 : 1 : 3-*tricarboxylic acid.* When prepared as above, but with diethyl malonate instead of methylmalonate, this acid had m. p. 122—123° (decomp.) (Found : C, 41·15; H, 4·8. Calc. for $C_6H_8O_6$: C, 40·9; H, 4·55%) (Dickens, Kon, and Thorpe, *J.*, 1922, **121**, 1502, give m. p. 123°).

2-*Phenylbutane*-1 : 3-*dicarboxylic acid.* Triethyl 2-phenylbutane-1 : 1 : 3-tricarboxylate (Michael and Ross, *loc. cit.*) (0·48 g.) was refluxed for 11 hr. with a mixture of water (5 ml.) and concentrated hydrochloric acid (5 ml.). The cooled solution was extracted with ether, the extract dried (Na_2SO_4), and the ether removed. A solution of the residue in chloroform was diluted with light petroleum (b. p. 40—60°) and stirred. The product (0·2 g.), separating from benzene–light petroleum, had m. p. 122—123° (Found : C, 64·35; H, 6·2. Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·3%) (Avery and Fossler, *Amer. Chem. J.*, 1898, **20**, 516, give m. p. 125°).

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Steric Hindrance in Aromatic Hydrocarbon Systems.

By H. O. Pritchard and F. H. Sumner.

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Using a very crude molecular-orbital model we have calculated the effect of the steric repulsion between non-bonded hydrogen atoms in the diphenylmethyl and triphenylmethyl radicals. It is assumed that each ring in, say, the triphenylmethyl radical is equally twisted through an angle θ with respect to the plane of the methyl carbon atom and that the resonance integral between two carbon atoms whose p_π-orbitals are twisted through an angle θ with respect to each other is given by $\beta \cos \theta$; thus we can calculate in terms of (the unknown) β the resonance energy of the triphenylmethyl radical for a series of angles by the conventional molecular-orbital treatment. We have also assumed that the repulsion between two non-bonded hydrogen atoms is closely similar to the $^3\Sigma H_2$ molecule potential-energy curve $V(r)$ proposed by Hirschfelder and Linnett (*J. Chem. Physics*, 1950, **18**, 130) and have used $nV(r)$ as a trial function (where $n < 1$). For the purposes of the present calculations β is taken to be -40 kcal./mole (a value giving approximately the correct resonance energy for the benzyl radical) and n is given the value 0·5; this is a reasonable combination of parameters as it leads to angles of twist in diphenyl and in triphenylbenzene of about 30°, to be compared with the experimental values of 45° ± 10° (Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408) and 30° ± 10° (Lonsdale, *Z. Krist.*, 1937, **97**, 91; Farag, *Acta Cryst.*, 1954, **7**, 117) respectively. The essential qualitative conclusions are unaffected by the choice of other pairs of values for β and n.

Radical	(E.R.E.)$_{\theta=0}$*	$\theta_{min.}$	E.R.E. at minimum (kcal.)	H–H repulsion at minimum (kcal.)	Corrected E.R.E. at minimum (kcal.)	Experimental E.R.E. (kcal.)
CH_2Ph	0·722β †	0°	0·722β = −28·9	0	−28·9	−24·5
$CHPh_2$	1·301β	49	1·112β = −44·5	3·3	−41·2	−30
CPh_3	1·800β	57	1·465β = −58·6	4·7	−53·9	−27

* E.R.E. = extra resonance energy over that of the phenyl rings.
† From Coulson, *Discuss. Faraday Soc.*, 1947, **2**, 9.

The (extra) resonance energies of the di- and the tri-phenylmethyl radical and of the benzyl radical are known (Szwarc, *Discuss. Faraday Soc.*, 1951, **10**, 336; Jaquiss, Thesis, Manchester, 1953), and these are compared with the calculated values in the Table; the calculated values are based on a C–H distance of 1·08 Å and the C–C distances given by the simple M.O. treatment (the allowance for the fact that the C–C bond lengths change slightly as the molecule is twisted only alters the calculated angle by a fraction of a degree and this effect can be ignored). It seems that β is a little too large, and that $\frac{1}{4}V(r)$ rather underestimates the repulsion energy; however, no reasonable choice for the repulsion energy brings the resonance energy of the triphenylmethyl radical below that of the diphenylmethyl radical. This suggests that the latter radical has other means of relieving the hydrogen–hydrogen repulsions, and it is evident that the diphenylmethyl radical is rather flatter than our calculations show, with the phenyl–C–phenyl angle significantly greater than the normal 120°.

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Manchester University. [*Received, November 6th*, 1954.]

The Ammonolysis of Methyl 2 : 3-Anhydro-D-lyxofuranoside.

By J. M. Anderson and Elizabeth Percival.

[Reprint Order No. 5857.]

Baker, Schaub, Joseph, and Williams (*J. Amer. Chem. Soc.*, 1954, **76**, 4044) in the course of a total synthesis of puromycin reported the isolation of the α- and the β-form of methyl 3-acetamido-3-deoxy-D-arabofuranoside by ammonolysis, followed by *N*-acetylation, of the methyl 2 : 3-anhydro-D-lyxofuranosides. In investigations into the mode of fission of ethylene oxide rings we too carried out this series of reactions and isolated the two anomers. Baker *et al.* (*loc. cit.*) concluded that their product was the 3-amino-3-deoxy-D-arabinose derivative and not the other possible fission product, the 2-amino-2-deoxy-D-xylose derivative, inasmuch as the hydrochloride of their product had a different decomposition point and rotation from 2-amino-2-deoxy-D-xylose hydrochloride, prepared by Wolfrom and Anno (*J. Amer. Chem. Soc.*, 1953, **75**, 1038). We obtained proof that neither of the crystalline *N*-acetyl derivatives was a xylose derivative because all attempts to condense them with acetone were unsuccessful. The starting material was obtained in quantitative yield in every experiment, whereas 2-amino-2-deoxy-D-xylose would have given the 3 : 5-*iso*propylidene derivative. It is clear therefore that the main product from the fission of the oxide ring is an arabinose derivative.

Proof that no change to the pyranose form had occurred was obtained by the isolation from both anomers of the di-*O*-toluene-*p*-sulphonyl derivative followed by replacement of the primary toluene-*p*-sulphonyloxy-group by iodine. The action of sodium iodide in acetone was carried out under conditions specific for the replacement of a toluene-*p*-sulphonyloxy-group attached to a primary carbon atom (see Tipson, *Adv. Carbohydrate Chem.*, 1954, **8**, 192). Control experiments were carried out with methyl 2 : 3 : 4-tri-*O*-benzoyl-6-*O*-toluene-*p*-sulphonyl-α-D-mannopyranoside and toluene-*p*-sulphonamide. The former gave the same percentage yield of sodium toluene-*p*-sulphonate as did the above di-*O*-toluene-*p*-sulphonyl derivatives; the latter gave no sodium toluene-*p*-sulphonate, evidence that had the toluene-*p*-sulphonyl chloride condensed with the amino-group of the sugar it would not be removed under these conditions.

Experimental.—Solvents were removed under reduced pressure. Methanolic ammonia was prepared by saturating dry methanol with ammonia at 0°.

Methyl 3-acetamido-3-deoxy-α-D-arabofuranoside. Methyl 2 : 3-anhydro-α-D-lyxofuranoside (*J.*, 1953, 564) (m. p. 80°; 0·90 g.), dissolved in dry methanolic ammonia (40 ml.), was heated in a sealed tube at 120° for 48 hr. After concentration of the cooled solution, distillation gave a viscous syrup (0·85 g.), b. p. 150—170°/0·01 mm. A solution of this in water (20 ml.) and methanol (2 ml.) was stirred at 5° with anion-exchange resin (Amberlite I.R. 400; bicarbonate form) (24 ml.) and acetic anhydride (0·6 ml.) for 90 min. (Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301). Filtration and evaporation gave a syrup (0·96 g.), which formed prisms (0·52 g.) from acetone, and on recrystallisation had m. p. 120—121°, $[\alpha]_D^{24}$ +124° (*c*, 0·7 in EtOH), +134° (*c*, 1·0 in H_2O) (Baker *et al.*, *loc. cit.*, record m. p. 115—116°, $[\alpha]_D$ +102° in H_2O) (Found: C, 47·2; H, 7·6; N, 6·5. Calc. for $C_8H_{17}O_5N$: C, 46·8; H, 7·4; N, 6·8%).

Methyl 3-acetamido-3-deoxy-β-D-arabofuranoside. Syrupy methyl 2 : 3-anhydro-αβ-D-lyxoside (2·8 g.), in dry methanolic ammonia (75 ml.), was treated as described for the α-form. A portion (1·01 g.) of the derived syrup in dry methanol (20 ml.) was treated with acetic anhydride (2·5 ml.), and the mixture kept at 18° for 18 hr. This, after dilution with water (10 ml.), neutralisation with solid sodium hydrogen carbonate, filtration, and evaporation to dryness, gave a residue which was extracted with chloroform. Evaporation of the dried chloroform extract gave a syrup (0·76 g.) which, on solution in methanol–acetone (50%), addition of ether to incipient turbidity and recrystallisation, yielded needles (0·16 g.), m. p. 156°, $[\alpha]_D^{18}$ −165° (*c*, 1·0 in EtOH), −120° (*c*, 1·2 in H_2O) (Baker *et al.*, record m. p. 155°, $[\alpha]_D$ −119° in H_2O) (Found: C, 46·2; H, 7·3; N, 6·9%).

Attempted isolation of an isopropylidene derivative. Methyl 3-acetamido-3-deoxy-α-D-arabofuranoside (50 mg.) was shaken with dry acetone (10 ml.), anhydrous copper sulphate (1 g.), and 2 drops of acetaldehyde for 14 days. This gave a syrup (45 mg.) which crystallised

completely on trituration with acetone; the solid had m. p. and mixed m. p. with starting material 118—120°, $[\alpha]_D^{18}$ +124° (*c*, 0·7 in EtOH). Methyl 3-acetamido-3-deoxy-β-D-arabofuranoside (50 mg.) was treated with dry acetone and anhydrous copper sulphate under the same conditions. The product (46 mg.) had m. p. and mixed m. p. with starting material 156°, $[\alpha]_D^{18}$ −160° (*c*, 0·5 in EtOH) (Found: C, 46·9; H, 7·35. Calc. for $C_8H_{17}O_5N$: C, 46·8; H, 7·4; for $C_{11}H_{19}O_5N$: C, 53·8; H, 7·8%).

Methyl 3-acetamido-3-deoxy-2:5-di-O-toluene-p-sulphonyl-α-D-arabofuranoside. Methyl 3-acetamido-3-deoxy-α-D-arabofuranoside (10 mg.) in dry pyridine (1 ml.) was treated with toluene-*p*-sulphonyl chloride (40 mg.) in the presence of "Drierite" for 60 hr. at room temperature. The toluene-*p*-sulphonyl derivative (11·7 μmoles) obtained after appropriate treatment, was dissolved in dry acetone and heated with sodium iodide in a sealed tube for 2 hr. at 100°. Characteristic plate-shaped crystals of sodium toluene-*p*-sulphonate (identified as the *S*-benzylthiouronium salt, m. p. 179—180°) were deposited in a yield (10·3 μmoles) comparable with that in a similar experiment carried out on methyl 2:3:4-tri-*O*-benzoyl-6-*O*-toluene-*p*-sulphonyl-α-D-mannopyranoside (9·3 μmoles from/11·4 μmoles). Toluene-*p*-sulphonamide failed to yield sodium toluene-*p*-sulphonate under similar treatment. Identical experiments were carried out with the β-anomer (10 mg.) and the derived 2:5-di-*O*-toluene-*p*-sulphonyl derivative (19·5 μmoles) on treatment with sodium iodide in acetone gave sodium toluene-*p*-sulphonate (16·5 μmoles). (Corrections for solubility of sodium toluene-*p*-sulphonate in acetone were made in all of these experiments.)

3-Amino-3-deoxy-D-arabinose hydrochloride. After methyl 3-acetamido-3-deoxy-α-D-arabofuranoside (91 mg.) had been heated at 100° with hydrochloric acid (10 ml.; 3N) for 60 min. and the solution had been concentrated to dryness, a syrup was obtained which crystallised from methanol; the solid had m. p. 161° (decomp.), $[\alpha]_D^{18}$ −109° (*c*, 0·3 in H_2O) {Baker *et al.*, *loc. cit.*, record m. p. 159° (decomp.), $[\alpha]_D$ −112° in H_2O}.

The authors are grateful to Professor E. L. Hirst, F.R.S., for advice and encouragement, and one of them (J. M. A.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, EDINBURGH. [*Received, November 8th*, 1954.]

A New Preparation of Glycol Monoesters of Fatty Acids.

By T. H. BEVAN, T. MALKIN, and D. B. SMITH.

[Reprint Order No. 5865.]

IN the preparation of glycol monoesters of fatty acids, either by direct esterification or by acylation, large amounts of diesters are formed even when great excess of glycol is used (cf. Hilditch and Rigg, *J.*, 1935, 1774), and, as the diesters are the less soluble, purification of the monoesters is difficult and wasteful. Verkade, Tollenaar, and Posthumus (*Rec. Trav. chim.*, 1942, **61**, 373) avoided diester formation by acylating the monotriphenylmethyl ether, and removing the triphenylmethyl group by catalytic hydrogenation. Baer, however (*J. Amer. Chem. Soc.*, 1953, **75**, 5533), claims to obtain high yields of monoester by direct acylation at −15°, in a mixture of dimethylformamide and chloroform. He states that the method of Verkade *et al.* is tedious, and that their products tenaciously hold traces of triphenylmethyl compounds. This van Gijzen and Verkade deny (*Rec. Trav. chim.*, 1954, **73**, 496) and point out that their products melt higher than those of Baer and are presumably purer.

In view of this disagreement, the following method will be of interest, since it gives higher yields than the above methods and avoids any possibility of diester formation. Ethylene iodohydrin is acylated, and the iodine atom is then replaced by hydroxyl, by refluxing with aqueous-alcoholic silver nitrite. Both stages go smoothly in 90—95% yield.

Fischer (*Ber.*, **1920**, **53**, 1621) used a similar method for the preparation of 1 : 3-diglycerides, but no explanation of the use of silver nitrite is given. In several cases that we have tried, silver nitrate acts equally well.

We have not studied the behaviour of acyl bromohydrins extensively, but 2-bromoethyl palmitate is converted into 2-hydroxyethyl palmitate in 77% yield.

Experimental.—*2-Iodoethyl palmitate.* Palmitoyl chloride (4·12 g., 0·015 mole) in dry benzene (15 ml.) was slowly added to ethylene iodohydrin (2·58 g., 0·015 mole) (Wieland and Sakellarios, *Ber.*, **1920**, **53**, 208) in dry benzene (10 ml.) containing dry pyridine (2 ml.) and left overnight. Ether was then added, and the ethereal solution was successively washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). After filtration and removal of ether, the *palmitate* crystallised from alcohol–ether as colourless platelets, m. p. 55° (5·6 g., 93%) (Found: C, 53·0; H, 8·7. $C_{18}H_{35}O_2I$ requires C, 52·7; H, 8·5%).

In the same way were made the *stearate* [from stearoyl chloride (7·4 g.) and iodohydrin (4·2 g.)] (10·2 g.), m. p. 62—63° (Found: C, 54·9; H, 8·9. $C_{20}H_{39}O_2I$ requires C, 54·8; H, 8·9%), *myristate* [8·2 g. from the chloride (5·6 g.) and iodohydrin (4 g.)], m. p. 46—47° (Found: C, 50·3; H, 8·1. $C_{16}H_{31}O_2I$ requires C, 50·3; H, 8·1%), and *laurate* [7·5 g. from the chloride (5·1 g.) and iodohydrin (4 g.)], m. p. 35—36° (Found: C, 47·5; H, 7·7. $C_{14}H_{27}O_2I$ requires C, 47·5; H, 7·6%).

2-Hydroxyethyl palmitate. The iodoethyl palmitate (2 g.) was refluxed with a solution of silver nitrite (2·5 g.) in ethanol (20 ml.) and water (2 ml.) for ¾ hr. The solution was then filtered hot, and the solvent was removed under reduced pressure The residue was shaken with warm light petroleum (b. p. 60—80°), which dissolved the hydroxyethyl ester, and after filtration it was kept at 0°. The product which separated was recrystallised from light petroleum and yielded colourless plates (1·4 g.), m. p. 52—53° (Found: C, 71·6; H, 11·9. Calc. for $C_{18}H_{36}O_3$: C, 72·0; H, 12·0%). Similarly were made the stearate, m. p. 60—61° (95%) (Found: C, 72·9; H, 12·2. Calc. for $C_{20}H_{40}O_3$: C, 73·1; H, 12·3%), myristate, m. p. 43—43·5° (93%) (Found: C, 70·4; H, 11·8. Calc. for $C_{16}H_{32}O_3$: C, 70·5; H, 11·8%), and laurate, m. p. 31—32° (91%) (Found: C, 69·0; H, 11·5. Calc. for $C_{14}H_{28}O_3$: C, 68·8; H, 11·6%).

2-Bromoethyl palmitate. Ethylene bromohydrin (1·9 g.) was acylated with palmitoyl chloride (4·2 g.) as described for palmitoyl iodohydrin, to give *2-bromoethyl palmitate* (4·85 g.), m. p. 45—46° (88%) (Found: C, 59·8; H, 9·8; Br, 22·0. $C_{18}H_{35}O_2Br$ requires C, 59·5; H, 9·7; Br, 22·0%). This ester, treated as described in the preparation of hydroxyethyl ester, except that more silver nitrite was used (3 g.), yielded monopalmitoyl glycol (1·3 g.), m. p. and mixed m. p. 52—53° (77%).

THE UNIVERSITY, BRISTOL, 8. [*Received, November 11th*, 1954.]

The Erythrophleum Alkaloids. Cassaic Acid.

By L. G. HUMBER and W. I. TAYLOR.

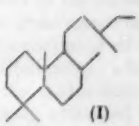
[Reprint Order No. 5895.]

THE Erythrophleum alkaloids are alkamine esters of diterpene monocarboxylic acids (see review by Dalma, "The Alkaloids," Vol. IV, edited by Manske and Holmes, Academic Press, New York, 1954, p. 265) which have remarkable cardiac activity coupled with intense local anæsthetic action. The most thoroughly investigated member is cassaine which on acid hydrolysis gave dimethylaminoethanol and cassaic acid, $C_{20}H_{30}O_4$, an αβ-unsaturated hydroxyketo-acid to which cassaidic, coumingic, and coumingidic acids are related. Hydrolysis of cassaine under basic conditions afforded a mixture of cassaic and *allo*cassaic acid (Dalma, *Helv. Chim. Acta*, **1939**, **22**, 1947; Ruzicka and Dalma, *ibid.*, p. 1517, footnote 2). The double bond of the latter was no longer conjugated with the carboxyl group and, since both acids yielded the same dihydrocassaic acid, it was evident that no rearrangement of the carbon skeleton had occurred. This behaviour resembles the conversion of *cyclo*hexylideneacetic acid (Kon and Linstead, *J.*, 1929, 1269), under

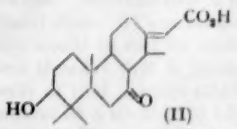
basic conditions, into an equilibrium mixture of *cyclo*hexylidene- and *cyclo*hex-1-enylacetic acid, the latter predominating. Thus we conclude that the carboxyl group in cassaic acid is in the side chain.

Ruzicka and his co-workers (Ruzicka, Engel, Ronco, and Berse, *Helv. Chim. Acta*, 1945, **28**, 1038; Engel, Ronco, Berse, Plattner, and Ruzicka, *ibid.*, 1949, **32**, 1713) oxidised dihydrocassaic acid to dioxocassanic acid, which on Wolff–Kischner reduction formed cassanic acid. Dehydrogenation of cassanic acid gave 1 : 2 : 8-trimethylphenanthrene. Methyl cassanate on treatment with methylmagnesium iodide followed by dehydration and dehydrogenation gave a hydrocarbon $C_{20}H_{22}$, which, if the carboxyl group of cassaic acid had been attached to the nucleus, must have been a 1 : 2 : 8-trimethyl-*x*-*iso*propylphenanthrene. Comparison of the ultra-violet absorption spectra of a number of synthetic alkylphenanthrenes with the $C_{20}H_{22}$ hydrocarbon led the above authors to conclude that their hydrocarbon was trisubstituted. Consequently the carboxyl group was in a side chain, and the $C_{20}H_{22}$ hydrocarbon must be an *iso*butyldimethylphenanthrene.

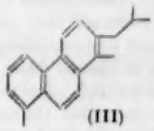
The known diterpene acids can all be derived from the hypothetical precursor (I) (the biogenetic isoprene rule of Ruzicka, *Experientia*, 1953, **9**, 366) so that if cassaic acid were (II) the $C_{20}H_{22}$ hydrocarbon should be (III).



(I)



(II)



(III)

We have synthesised (III) from 1 : 8-dimethylphenanthrene taking advantage of the fact that acylation of a dihydrophenanthrene proceeds exclusively in the 2-position. The ultra-violet absorption spectrum and melting point of the resulting hydrocarbon, and the melting point of its trinitrobenzene derivative, were identical with those recorded for the $C_{20}H_{22}$ hydrocarbon and its derivative (Ruzicka, Engel, Ronco, and Berse, *loc. cit.*); this establishes the carbon skeleton of cassaic acid as in (II).

The ultra-violet absorption spectrum (Ruzicka and Dalma, *loc. cit.*) of dioxocassaic acid ($\lambda_{max.}$ 223 mμ; log ε 4·2) is typical of an αβ-unsaturated acid and shows the absence of 1 : 2- and 1 : 3-dioxo-groupings, an αβ-unsaturated ketone, and the grouping ·CO·CH:CH·CO_2H; therefore the secondary oxygen functions cannot be in the same rings. Ring C appears to be excluded as a site for one of the oxygen atoms and we favour as a working hypothesis the groupings shown in (II).

Note Added February 9th, 1955.—Dr. B. Engel has kindly shown that our synthetic hydrocarbon (III) does not depress the melting point of the $C_{20}H_{22}$ compound. He has also informed us that by ozonolysis of dioxocassaic acid he has obtained oxalic acid (70%) and a trioxo-compound whose ultraviolet spectrum indicated isolated ketonic groups only, giving additional support to our deductions. The possibility that cassaic acid has the carbon skeleton shown in (II) has been indicated earlier by R. Tondeur (Ph.D. Thesis; E.T.H., Zurich, 1950) and we thank Dr. Engel for this information.

Experimental.—**9 : 10-*Dihydro*-1 : 8-*dimethylphenanthrene*.** Sodium (2·5 g.) was added during 30 min. to 1 : 8-dimethylphenanthrene (2·3 g.) in boiling amyl alcohol. The cooled mixture was shaken with water, and the organic layer washed until neutral and then concentrated. The oil (2·25 g.) was chromatographed on activated alumina; the light petroleum (b. p. 60—80°) eluate gave the ***dihydrophenanthrene***, m. p. 144—146° (from ethanol), $\lambda_{max.}$ 270 mμ (log ε 4·07) (Found, in a sublimed sample: C, 92·2; H, 7·8. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%).

2-iso*Butyryl*-9 : 10-*dihydro*-1 : 8-*dimethylphenanthrene*. *iso*Butyryl chloride (140 mg.) and aluminium chloride (310 mg.) in nitrobenzene (5 ml.) were added successively to the dihydrophenanthrene (240 mg.) in nitrobenzene (5 ml.), and the mixture kept at 0° for 4 hr. then at room temperature for 3 hr. It was poured on cracked ice, and the nitrobenzene solution washed well with water and then concentrated to a red oil (330 mg.) which was chromatographed on activated alumina. The light petroleum eluate gave the ***ketone***, m. p. 93—94° (from light

petroleum), $\lambda_{max.}$ 290 mμ (log ε 4·20) (Found in a sample dried at 50° *in vacuo*: C, 86·3; H, 7·9. $C_{30}H_{32}O$ requires C, 86·4; H, 7·9%).

2-iso*Butyl*-1 : 8-*dimethylphenanthrene*. A solution of the above dihydrophenanthrene (145 mg.) in dilute hydrochloric acid and ethanol was refluxed for 76 hr. with amalgamated zinc (1·5 g.), periodic additions of concentrated hydrochloric acid (5 ml.) being made. Exhaustive extraction with ether furnished the crude trialkyldihydrophenanthrene (140 mg.) which was heated at 350° for 15 min. with selenium (200 mg.). The solidified mass was extracted (Soxhlet) with benzene, and the product was chromatographed in light petroleum over activated alumina. The light petroleum eluate crystallised readily from methanol to give 2-iso*butyl*-1 : 8-*dimethylphenanthrene* (120 mg.), m. p. 131°, $\lambda_{max.}$ 254, 262, 284, 294, 306, 322, and 338 mμ (log ε 4·58, 4·83, 4·04, 4·00, 4·07, 2·57, and 2·48) (Found, in a sublimed sample: C, 91·7; H, 8·5. $C_{20}H_{22}$ requires C, 91·6; H, 8·5%). The yellow *trinitrobenzene derivative* had m. p. 131—132° (from ethanol) (Found, in a specimen dried at 70° for 12 hr. *in vacuo*: C, 65·7; H, 5·3. $C_{20}H_{22},C_6H_3O_6N_3$ requires C, 65·7; N, 5·3%).

We are indebted to the National Research Council of Canada for a grant.

UNIVERSITY OF NEW BRUNSWICK. [*Received, November 20th*, 1954.]

OBITUARY NOTICE.

JOHN EDWARD LENNARD-JONES.

1894—1954.

By the death of John Edward Lennard-Jones, on November 1st, 1954, the world has suffered the loss of an eminent theoretical chemist and an able administrator. Lennard-Jones was born on October 27th, 1894, and was educated at Manchester University and at Trinity College, Cambridge. On the outbreak of the first world war he became a pilot flying officer in the Royal Flying Corps and later served as experimental officer at the Armament Experimental Station, Orfordness.

In 1919 he returned as lecturer in mathematics to his old university of Manchester. From thence he migrated to Bristol University as Reader in Mathematical Physics and later, in 1925, was appointed as the first holder of the Chair in Theoretical Physics at that University. In the same year he married Kathleen Mary, daughter of the late Alderman S. Lennard of Leicester.

During the years 1930 to 1932 he was Dean of the Faculty of Science in Bristol. In 1930 the University of Cambridge was given a generous bequest by John Humphrey Plummer to endow three new chairs in the faculty of science. By 1932 two of these chairs had already been filled and discussion arose concerning the third chair. It was believed by many that the most pressing needs of the Department of Chemistry would be met by making an appointment in the subject of Inorganic Chemistry, whilst others thought that it would receive most benefit if someone interested in the mathematical aspects of that Science could be appointed. Lennard-Jones's work had already attracted the attention of a number of physical chemists and eventually he was elected as the first John Humphrey Plummer Professor of Theoretical Chemistry and Professorial Fellow of Corpus Christi College. In retrospect, no one in the University of Cambridge can regret what was considered at the time to be a somewhat daring experiment.

During the 1939—45 war, and subsequently, he was closely associated with the work of the Ministry of Supply, particularly in the field of Armament Research; thus from 1940 onwards, he served on several Committees of the Minister's Scientific Advisory Council and from the beginning of 1942 on that Council itself.

In the Autumn of 1942, he was appointed to the responsible and onerous post of Chief Superintendent of the Armament Research Establishment, a position which he held until the end of the War.

In August, 1945, he became Director-General of Scientific Research in the Ministry and played a very active part in the planning and re-organisation of the scientific effort consequent upon the change-over to peace-time conditions and the amalgamation of the war-time Ministries of Supply and Aircraft Production. During this period he was also active in the reorganisation of the Minister's Scientific Advisory Council to suit peace-time conditions.

In October, 1946, Sir John returned to Cambridge but did not cease his interest in Defence Research as he became Chairman of the Minister's Scientific Advisory Council in 1947, a duty which he carried out with his usual high standards of ability and thoroughness until 1953.

From 1942 to 1947 he was a member of the Advisory Council of the Department of Scientific and Industrial Research and of the Scientific Advisory Committee of the National Gallery. He was President of the Faraday Society in the years 1948—1950 and was elected a Fellow of the Royal Society in 1933, on the Council of which he sat during the years 1941—1943.

The death of Lord Lindsay of Birker, the first principal of the new University College of North Staffordshire, left vacant an administrative post at Keele, one of extraordinary interest but full of the novel problems always associated with the development of an educational experiment on new lines. Lennard-Jones was asked to fill this difficult post which he gladly accepted in April, 1953, and was entering on his new work with enthusiasm and interest until his death. He was a D.Sc. of Manchester, and Sc.D. of Cambridge, and was awarded the K.B.E. in 1946 and the Davy Medal of the Royal Society in 1953. Just before his death, as President of Section B of the British Association at Oxford, he was given an honorary degree of that university and a little later, the Chemical Society gave him their highest award—the Longstaff Medal. He is survived by his widow, son, and daughter.

Naturally a great deal of Lennard-Jones's contributions to science are less significant to chemists than to physicists but in the field of theoretical chemistry he has made several outstanding contributions. The determination of the nature of intermolecular potential energies

from the experimental second and third virial coefficients of the compressibilities of gases had long been the subject of detailed examination; the work of Keesom being regarded as classical in this field. The modern phase of the subject began in 1924 when Lennard-Jones, using a soft-sphere model, introduced his well-known semi-empirical law for the intermolecular potential $E(r)$:

$$E(r) = \frac{a}{r^n} - \frac{b}{r^m}$$

When n and m are assigned the values of 6 and 12, the calculated expression for the second virial of many gases fits the data within experimental accuracy. Several of the diatomic gases also, such as H_2 and N_2, and also CH_4, likewise conform closely in their properties given by this equation; and extensions to molecules of cylindrical symmetry such as CO_2, C_2H_4, and C_2H_2 have been made by several of his junior colleagues.

The theory of Frenkel and Eyring that a liquid contained vacant sites or holes likewise received Lennard-Jones's attention. Eyring and his co-workers were led to the assumption that a molecule of liquid was confined in a small volume of the surrounding molecules but that within this volume the molecule was free to move under the combined forces of the neighbours which confined it in its cell. Lennard-Jones showed that with values of n and m taken as 7 and 13, respectively, a molecule moving in a field of twelve neighbours would have nearly constant potential energy over a large part of the cell. He then went on to consider fusion as an order–disorder transition, visualising the existence of two interpenetrating lattices of atoms and holes respectively; the interatomic forces tend to produce an orderly alternation of lattice points whilst the entropy tends to produce a disordered arrangement. The forces involved are both of long range and of short range; on expansion of the lattice the long-range forces disappear first and at this stage fusion occurs. At Cambridge he took a great interest in the experimental work going on in the laboratories and finding that the subject of adsorption and heterogeneous catalysis was receiving a great deal of attention he devoted much time and thought to the examination of the problems involved. No less than twelve papers were devoted to developing a fundamental theory of adsorption kinetics. Simple considerations permit one to obtain the value of the product $\alpha\tau$ involving the accommodation coefficient of a gas striking a surface and its lifetime in the adsorbed phase. Lennard-Jones obtained expressions for these constants in terms of the physical properties of the solid and its surface field. He determined, *inter alia*, the free surface energy of the surfaces of heteropolar crystals, and the conditions for surface migration, and obtained an expression for the interaction energy of a metal surface with a non-polar molecule. He initiated the development of a mathematical laboratory and installed one of the first computing machines, encouraging the experimentalists to make free use of it.

He initiated, when at Bristol, his life-long enquiry into the wave-mechanical aspects of molecular structure, developing the concept of molecular orbitals. In his first paper, a classic in this field, he brought out in a simple way the mathematical implications of the experimental studies of quantum numbers in molecules made by R. S. Mulliken and others. The central idea here is that each bonding electron moves in some form of orbit, similar to the situation in atoms except that the molecular orbits are polycentric instead of monocentric. In the exceedingly important field of aromatic and condensed molecules, Lennard-Jones made valuable contributions to our knowledge of the behaviour of the π-electrons, and showed in particular how quite small differences between C–C bond lengths may be attributed to their influence. This work he continued at Cambridge and his most recent papers describe the theory of transformation between molecular and equivalent orbitals for symmetrical molecules, equivalent orbitals being regarded sometimes as bond orbitals around a central atom and at other times as associated with a bond between two atoms—the concept made use of by Slater and Pauling.

"L. J." to his many friends and "Ted" to a few, Lennard-Jones always had time to discuss problems of mutual interest and would take both trouble and time in helping to solve them. He loved the open air and was most knowledgeable on bird lore and was probably at his happiest in taking long country walks. No more fitting description of his personality can be given than in those words written by Chaucer:

> A knight ther was, and that a worthy man,
> That fro the tyme that he first bigan
> To ryden out, he loved chivalrye,
> Trouthe and honour, fredom and curteisye.
> He nevere yet no vileinye ne sayde
> In al his lyf un-to no maner wight.
> He was a verray purfit knight.

ERIC K. RIDEAL.

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